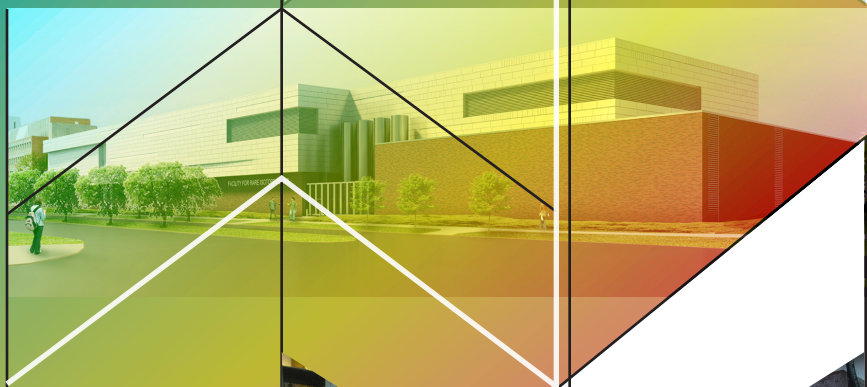
MEETING ISOTOPE NEEDS AND CAPTURING OPPORTUNITIES FOR THE FUTURE:

THE 2015 LONG RANGE PLAN FOR THE DOE-NP ISOTOPE PROGRAM



NSAC ISOTOPES SUBCOMMITTEE

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Meeting Isotope Needs and Capturing Opportunities for the Future: The 2015 Long Range Plan for the DOE-NP Isotope Program

NSAC Isotopes Subcommittee
July 20, 2015

About the Cover: The cover represents the varied facets of the DOE Isotope Program. The backbone of the program is the chemical elements, which come with varying atomic weights called isotopes. The lower part of the cover shows a chart of the isotopes where each row is an element and each square in the row represents an isotope. The color code is by half-life. The cover illustrates the wide range and importance of isotopes to the Nation, with examples from biology and medicine, physical sciences and chemistry, and national security and engineering. Illustrated at the center right are two keys to the program: the skilled workforce and continuing advances in technology, (epitomized in this photo by a new science user facility, FRIB, under construction). Upper right: ^{124}I PET images of a patient before and after the administration of the cancer drug selumetinib, which causes increased uptake of radio-iodine into metastatic thyroid cancer. In this theranostic isotope pair, increased uptake of the ^{124}I provides the PET image documentation of the beneficial effect, while increased uptake of ^{131}I kills the cancer cells. Upper left: Image of the sample of ^{249}Bk, made at the High Flux Isotope Reactor (HFIR) at DOE's Oak Ridge National Laboratory for the experiment that discovered element 117. Left middle: The isotope ^{3}He is use in portal monitors to detect illicit nuclear material in trucks crossing the U.S. border. Center: ^{68}Ga DOTATOC PET scan illustrating radiopharmaceutical uptake in several metastatic tumor sites. Cover art by Erin O'Donnell. The images of the scientist and the facility are courtesy of BNL and MSU, respectively. The attributions for the other images can be found in their captions where they appear (along with more detailed explanations) in the body of this document.

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Executive Summary

The Isotope Program within the Department of Energy (DOE), formally known as the Isotope Development and Production for Research and Applications Program (IDPRA), is managed by the DOE Office of Science's Office of Nuclear Physics (DOE-NP). IDPRA was created in 2009, when the Isotope Program was transferred from the DOE Office of Nuclear Energy to the Office of Nuclear Physics. Among the actions taken in preparation for that transfer, DOE-NP requested that the Nuclear Science Advisory Committee (NSAC) establish the NSAC Isotope (NSACI) subcommittee to advise it on specific questions concerning the Isotope Program. NSACI was asked: to identify and prioritize the compelling research opportunities using isotopes; to study the opportunities and priorities for ensuring a robust national program in isotope production and development; and to recommend a long-term strategic plan that will provide a framework for a coordinated implementation of IDPRA.

The two 2009 NSACI reports [NSACI09, NSACI09A] set the course for IDPRA, with recommendations on: how it should be organized and conduct business; investments that needed to be made in development of a highly-trained workforce for the future; investments that needed to be made in production capability; and compelling research opportunities. It is clear that the Isotope Program has been pursuing these recommendations vigorously and to great effect in the intervening half-dozen years.

In April 2014, NSAC was asked to re-establish NSACI and requested that it: develop an updated Long-Range Strategic Plan for the Isotope Program; articulate the progress made by the Isotope Program toward the goals set by the 2009 NSACI reports; update and prioritize compelling opportunities for the Program; and indicate what resources would be needed in the timeframe 2016-2025 to increase the domestic availability of isotopes appropriate to the DOE Isotope Program portfolio and deemed to be critical for the Nation. This report provides our response to the charge.

The NSACI subcommittee membership was again chosen to have broad representation from the research, industrial, and homeland security communities. In addition, one third of the members were also on the 2009 NSACI, providing important points of reference for our evaluation of the progress of IDPRA in meeting the goals set in 2009. The subcommittee heard presentations and/or received written input from a large number of federal institutions, professional societies, industry trade groups, and individual experts who were contacted for input (See Appendix 4).

The mission of the DOE Isotope Program, as expressed by its Director, Dr. Jehanne Gillo, at our first meeting, is threefold:

- Produce and/or distribute radioactive and stable isotopes that are in short supply, associated byproducts, surplus materials, and related isotope services;
- Maintain the infrastructure required to produce and supply isotope products and related services; and
- Conduct R&D on new and improved isotope production and processing techniques that can make available new isotopes for research and applications.

The Isotope Program is a relatively small federal program (FY15 federal appropriation of $19.84M and anticipated FY15 isotope sales of ~$36M) that enables and is immersed in billion-dollar enterprises, including medical diagnosis and treatment, research, national security, and critical industries. These applications touch the lives of almost every citizen. The potential benefits of expanded availability of key isotopes are substantial. In this report, the high priority opportunities are identified in the broad areas of: Biology, Medicine and Pharmaceuticals; Physical Sciences and Engineering; and National Security and Applications. Addressing these opportunities effectively, and assuring an increase in the domestic availability of isotopes deemed to be critical for the Nation, will require augmentation of both IDPRA's R&D budget and its current isotope delivery capabilities.

As was the case in 2009, the responsibility for the production of certain isotopes does not reside with IDPRA. These include: commercially produced isotopes that meet the demands of the Nation; isotopes for reactor fuels; and isotopes for weapons. DOE/NNSA also has the lead responsibility for the conversion of the commercial production of ^{99}Mo (the parent isotope of the most commonly used isotope in medical procedures, ^{99m}Tc) away from processes using highly-enriched uranium. The ^{99}Mo situation is summarized in Sidebar 9 in Chapter 5, and has been reviewed recently by both the U.S. and Canadian governments and the International Atomic Energy Agency (IAEA) [NSAC14, GC14, IAEA13]. Because ^{99}Mo and ^{99m}Tc are the responsibility of DOE/NNSA, and the supply situation is being reviewed regularly by others (as well as by a separate NSAC subcommittee), we (NSACI) have again refrained from reviewing the situation with this particular isotope.

Progress Made by IDPRA toward the Goals Set by the 2009 NSACI Reports

The two reports of the 2009 Nuclear Science Advisory Committee Isotopes Subcommittee made a total of 15 recommendations [NSACI09, NSACI09A]. The recommendations were organized into four categories: six compelling research opportunities; six recommendations for enhancing the effectiveness and efficiency of operations; one on the development of a highly trained workforce for the future; and two recommendations for major investments in production capability. The recommendations and the details of IDPRA's response and our evaluation of it are presented in Chapter 9. DOE-NP has done an outstanding job of reorganizing the program and setting it on a firm footing. The DOE Isotope Program now in place has realized the vision of the 2009 subcommittee and is making substantial progress toward expanding that vision. Key structures and processes are in place that have greatly enhanced DOE's productivity and impact on isotopes, and these should be continued and improved in the broad directions that have been established. The recommendations we make in this report build on the successes of IDPRA, encourage the completion of investments in production capability set in motion in response to the 2009 recommendations, and enhance the Isotope Program's ability to realize exciting opportunities presented by ongoing R&D on isotope uses.

The Strategic Plan

The Strategic Plan presented in this document builds on the original Strategic Plan developed by the 2009 NSACI subcommittee [NSACI09A], and on the realization of the critical points of that plan by the Office of Nuclear Physics. Specifically, our formal recommendations, which each appear in the relevant section(s) of our report, are listed here in priority order.

Recommendations

1) We recommend a significant increase of funding for Research and Development

Increased R&D is essential for an optimal Isotope Program. Increased R&D is necessary to fully realize the promise of enhanced national security, improved health care, and increased industrial competitiveness the program could provide. It will also support the expansion of the range and quantities of isotopes available for researchers and for potential commercial application, and enhance their usefulness to the Nation. It will support the development of more efficient techniques for their production, reducing costs and ensuring that supplies meet demands. R&D is also a core component of the program, enabling it to better weather fluctuations in revenues (funding) as isotopes transition to the commercial market and as foreign supplies vary. In addition to establishing optimal base R&D funding at the production sites, the increase will facilitate annual (rather than biennial) Funding Opportunity Announcements (FOAs) to be issued, allowing the program to identify and respond more rapidly to new ideas. This increase will allow the program to effectively support promising new areas as they arise. Four representative areas that would benefit today from increased R&D support are:

a) ***Continue support for R&D on the production of alpha-emitting radioisotopes –*** The lack of availability of alpha-emitting radioisotopes was identified in 2009 as a major limitation in the otherwise promising investigations of their potential for cancer therapy. Since the 2009 recommendation, the effectiveness of this novel therapy for cancer treatment has been demonstrated with FDA approval of the alpha emitter ^{223}Ra for metastatic bone cancer from hormone refractory prostate cancer. There has been significant progress made by the DOE Isotope Program in the development and production of some medically useful alpha-emitting isotopes in the past five years, but further research into new production methods, more efficient isolation methods, and automation of the isolation processes is needed to provide adequate availability of alpha-emitting radioisotopes for preclinical and clinical evaluations of this very promising therapy. A focus should continue on production of ^{225}Ac and ^{211}At. In addition, other alpha-emitting radioisotopes that may be applicable for treatment of other types of cancers, or for use in treating bacterial and viral infections are interesting. Thus, research into methods for production/isolation of alpha-emitters with shorter half-lives (e.g. ^{212}Pb/^{212}Bi, ^{213}Bi, and ^{226}Th) and longer half-lives (e.g. ^{227}Th) should also be a priority.

b) ***Support R&D into the production of high specific activity theranostic radioisotopes –*** Medical procedures that can be tailored to an individual's unique response will be more effective and lower the cost of health care**.** The move towards personalized medicine will be facilitated by supporting research on the production of radioisotopes, and isotopic pairs of the same element, that have both imaging and therapeutic emissions. Such agents, termed theranostic agents, can be used to obtain valuable pharmacokinetic and disease-targeting information in real time, which can allow rapid determination of whether the therapeutic approach will be effective in a specific patient. A requirement for theranostic radioisotopes produced for medical use is that they have very low quantities of other isotopes of that element present (or "high specific activity") after production and isolation. Personalized medicine will use highly specific targeting of diseased cells in

patients to differentiate their disease and help identify treatments that will be effective. High specific activity radioisotopes are required so that the targeted receptor or cell-surface antigen on the diseased cells are bound with targeting agents containing only, or mostly, the theranostic radioisotope. If low specific activity radioisotopes are used, the disease-targeting agent containing a stable isotope (or non-useful radioisotope) can compete for the receptor or antigen, dramatically decreasing binding of the isotope that provides the diagnostic and/or therapeutic emissions. This can lead to inconclusive imaging results and ineffective therapy.

c) ***Continue support for R&D on the use of electron accelerators for isotope production*** – Many isotopes that have ideal properties for applications in nuclear medicine and national security cannot currently be produced in the quantities and purity required. One of the major driving forces for new radioisotope production R&D is the need for increased yield and high specific activity. One of the newer approaches is the use of photons to initiate isotope production. While the concept has been around for decades, sources of photons with sufficient energy and flux to make the approach practical have only recently become available (through R&D driven by Basic Energy Sciences' need for high beam currents), so it is now possible to explore this pathway.

While the (γ,n) reaction is the mostly widely discussed, additional reactions could be examined, including (γ,p) and photofission. The (γ,p) reaction affords the possibility for producing radionuclides with high specific activity. The ^{68}Zn(γ,p)^{67}Cu reaction, where the copper isotope can be chemically separated from the target material, could be a viable route to this potential theranostic isotope (paired with ^{64}Cu). Other potential reactions of interest include; ^{232}Th(γ,spall)^{225}Ac, and ^{232}Th(γ,spall)^{211}Rn($t_{1/2}$=14.6 h, *EC*)^{211}At. These reactions are especially promising if multiple electron machines can be made available at reasonable costs. The photofission yield distribution from ^{238}U is almost identical to the thermal neutron fission of ^{235}U. This is a possible route to isotopes produced by fission that would remove the need for ^{235}U.

d) ***Support R&D on the development of irradiation materials for targets that will be exposed to extreme environments to take full advantage of the current suite of accelerator and reactor irradiation facilities –*** It is paramount that the production of critical radioisotopes be performed in a way that ensures public safety and protects the environment. The planned upgrades in production capacity at the isotope production accelerator facilities will create demands on the materials used and will likely require the development of new materials that can withstand high temperature and radiation conditions. In a similar manner, development in ion source feedstocks for use in the proposed radioactive separation system will be required to make full use of the new capacity available with the construction of this new system outlined in recommendation 3b.

2) We recommend completion and the establishment of effective, full intensity operations of the stable isotope separation capability at ORNL

The subcommittee is pleased with the progress that has been made since the 2009 NSACI recommendation toward the establishment of a stable isotope separation capability. Without this effort the U.S. is dependent on foreign sources for materials critical to the health and safety of the nation. This ongoing effort should continue until the separation capability has been fully established, the intensity goal of throughput comparable to a calutron (~100 mA ion current) has been achieved, and the separator is available for routine use. To achieve the goal for separator throughput, the Isotope Program is investing in the development of new ion source technology.

This facility will provide a reliable U.S. source of high-purity stable isotopes, many of which are currently available only from Russia, and will require, among other things, the allocation of a base operations budget for the separator.

3) We recommend an increase in the annual appropriated budget to realize the opportunities associated with high-impact infrastructure investments and to maintain a stable funding base for reliably operating and continually improving facilities. Specific opportunities for the period covered by this Long Range Plan include:

a) ***Infrastructure for isotope harvesting at FRIB -*** During routine operation for its nuclear physics mission, FRIB will produce a broad variety of isotopes that could be harvested synergistically without interference to the primary user. Research quantities of many of these isotopes, which are of interest to various applications including medicine, stockpile stewardship and astrophysics, are currently in short supply or have no source other than FRIB operation. The technical and economic viability of this proposed capability should be developed and assessed promptly.

b) ***Develop a strategy for the re-establishment of a separator for radioactive isotopes to support research*** – The isotope community has expressed the need for high specific activity, mass separated radioactive isotopes. A strategy for establishing a domestic capability for high purity radioactive isotopes should be developed. This capability is important to physical science programs, the medical community, and our national security. While chemical techniques can be used to separate the desired radioisotope from other elements, the selectivity to gain the isotopic purity desired by the community cannot be achieved without the development of electromagnetic separators for radioactive materials.

c) ***Increase the base infrastructure budget to sustain and expand production capacity at the Isotope Program facilities. Two near-term opportunities that merit support from this increased funding are:***

i) ***BNL Intensity upgrade and implementation of a second target station –*** Ongoing accelerator improvement projects at BLIP (installation of a beam Raster system and phase I of the Linac intensity upgrade) are expected to increase yields of ^{82}Sr. Phase I

of the Linac intensity upgrade will include an assessment of the feasibility of a second doubling of the intensity of the Linac. If feasible, continued increases in intensity could further increase isotope production yields and have much merit. The Radiation Effects Facility (REF) is a spur off the BLIP beam line that could be used to provide a 2^{nd} beam line at BLIP primarily for research irradiations. In this manner, research irradiations could be performed without interfering with ongoing large scale isotope production in the existing BLIP facility, providing more flexibility.

ii) ***Intensity, stability, and energy upgrades at LANL –*** While DOE has made critical infrastructure investments at LANL over the last five years, especially in the hot cell facility (including electrical and HVAC upgrades funded as separate upgrades efforts), this facility is nearing 50 years in age and will require additional investments to ensure continued reliable operations.

4) **We recommend continuation and expansion of the effort to integrate the university facilities with the Isotope Program**

The effort to form a network of university facilities that work with the DOE Isotope Program is commended and should be continued. University facilities have the ability to cost-effectively augment the capabilities of the national laboratories, and to meet demands for radioisotopes and radioisotope R&D that are not possible at the national laboratories, such as regional production of short-lived radioisotopes (e.g. ^{211}At) and evaluation of some alternative methods for radioisotope production. Partnership with university sites can also provide complementary and/or supplemental capabilities for production of isotopes where demands are not currently being met. The possibilities should continue to be evaluated on a site-by-site basis, in view of the differing capabilities of the universities. Several universities already provide radioisotopes that meet national needs, either by supplying commercial sources or making radioisotopes that are not readily available from commercial suppliers. Continuing exploration of how these university radioisotope producers can work with the DOE Isotope Program and how DOE could support university infrastructure and operations without compromising the Isotope Program or the current university production and distribution network is viewed as challenging, but very important, as coordination of this effort with the Isotope Program would improve the availability of key isotopes. Other university facilities do not yet produce isotopes in significant quantity and are likely to need improvements in infrastructure and equipment. The Isotope Program should continue to consider infrastructure upgrades to university facilities to produce isotopes to meet specific national needs. It is recognized that the degree of integration and the details of the interfaces of each university facility into the DOE Isotope Program will vary by site and circumstances. Finally, an important additional benefit of a DOE-university site partnership is the workforce training opportunity. It is recognized that these training opportunities are currently an important part of the Isotope Program and it is strongly recommended that they be continued.

Operations

We note that the Isotope Program has made dramatic improvements in operations in response to the recommendations of the 2009 Long Range Plan. As discussed in Chapter 9: Program Operations, it is essential that the practices, procedures, and key programs put in place continue.

Key areas where continued emphasis will be essential for continued progress are: communication, transportation, workforce development, public/private partnerships, foreign supply, and strategic planning. We summarize these areas below (and provide further details in Chapter 9.C):

Communication: Continued excellence in communication will enable the program to nimbly respond to the diverse isotope needs of the Nation. It will be important to maintain the continuous dialogue with interested federal agencies, international suppliers, and commercial isotope customers to forecast and match realistic isotope demand and achievable production capabilities. *Transportation:* The Transportation Working Group in the National Isotope Development Center (NIDC) must continue to work toward improvements in the ability to safely, efficiently, and cost-effectively transport radioactive isotopes both nationally and internationally. *Workforce Development:* Investments in workforce development to educate and train the next generation of nuclear scientists focused on isotope production should continue to be a priority. Funding university programs at all levels enables a highly trained workforce and can also generate new technologies and ideas. Working together with other DOE-SC programs to expose outstanding undergraduates to nuclear science and radiochemistry has proven to be an important path for attracting young scientists and engineers to the field. *Public/private partnerships*: Evolving public/private partnerships are a promising and cost-effective alternative to the construction of a dedicated accelerator for isotope production recommended by the 2009 NSAC; these opportunities should continue to be pursued. *Foreign supply:* The Isotope Program must continue its effort to identify critical isotopes for which the primary supply is from foreign sources and to develop mitigation strategies, as appropriate, to minimize supply constraints and disruptions. *Strategic planning:* Finally, strategic planning for isotopes as they transition from R&D to commercial sales, and communication with the users of these isotopes will continue to be a priority for the Isotope Program, and to be important for the long-term viability of the program.

Budget Implications of the Recommendations

Implementation of these recommendations is required to increase the domestic availability of isotopes appropriate to the DOE Isotope Program and deemed critical to the Nation. It would go a long way toward achieving an optimal Isotope Program, and to maintain the United States' leadership in a broad range of areas including medical treatments, basic research, and engineering/industrial applications of isotopes. It will further strengthen our national security in key areas of detection and analysis of threats. The subcommittee recommends an optimum appropriated budget that begins with the continuation of the present base operating funding of about $20M per year (FY2015$), which provides support for mission readiness and modest R&D efforts. This budget is currently supplemented by revenue from isotope sales (on a cost-recovery basis) of about $36M per year to support the production and distribution of isotopes, bringing the total IDPRA budget to $56M/year. This budget should then be augmented by an additional $19.5M per year (FY2015 dollars) of appropriated funds to fully implement our recommendations. This includes increases of: a total of $4M/year for high-priority R&D ($2M/year for an increased level of peer-reviewed R&D and $2M for the R&D programs carried out at the various DOE production sites); $2M/year to operate the stable isotope separation facility nearing completion at ORNL; a total of up to $13.5M/year to address a broad array of infrastructure needs and new opportunities including initiatives to strengthen the capabilities of

university facilities in the field (identified for the period of this Long Range Plan and anticipated as continuing needs beyond that period). Timing of funds to build the infrastructure for harvesting of isotopes at FRIB should allow this capability to be completed prior to FRIB operation, while the timing of funds for the construction of a radioisotope separator is less critical. Infrastructure upgrades at LANL, BNL, and ORNL continue throughout the period.

Our appropriated budget level we recommend is what is required to meet the program infrastructure needs and maintain that infrastructure at the cutting edge of the science. It is also essential to take advantage of R&D opportunities that will enhance the productivity of the entire program and speed the translation of exciting research directions in the application of isotopes to reality. If the needed increase over the FY2015 funding levels is not realized in the 2016-2025 time frame, critical infrastructure will decay, and opportunities needed to sustain and ultimately increase the supply and variety of key isotopes will not be realized. Furthermore, the R&D necessary for the future health of the program will not be performed, and the future of the trained workforce necessary for all aspects of isotopes will be at risk. Outstanding opportunities, such as establishing a domestic stable isotope program and engaging the Nation's network of university production capabilities will be jeopardized. The leadership of the United States in this area will be lost.

Chapter 1: Introduction

The Isotope Program within the Department of Energy (DOE), formally known as the Isotope Development and Production for Research and Applications Program (IDPRA), is managed by the DOE Office of Science's Office of Nuclear Physics (DOE-NP). IDPRA was created in 2009, when the Isotope Program was transferred from the DOE Office of Nuclear Energy. Among the actions taken in preparation for that transfer, DOE-NP requested that the Nuclear Science Advisory Committee (NSAC) establish the NSAC Isotope (NSACI) subcommittee to advise it on specific questions concerning the Isotope Program. NSACI was asked: to identify and prioritize the compelling research opportunities using isotopes; and to study the opportunities and priorities for ensuring a robust national program in isotope production and development, and to recommend a long-term strategic plan that will provide a framework for a coordinated implementation of IDPRA. The two 2009 NSACI reports [NSACI09, NSACI09A] set the course for IDPRA, making recommendations on: how it should be organized and conduct business; investments that needed to be made in development of a highly-trained workforce for the future; investments that needed to be made in production capability; and compelling research opportunities. It is clear that IDPRA has been pursuing these recommendations vigorously in the intervening half dozen years.

In April 2014, NSAC was asked to re-establish NSACI charge it to:

- Conduct a new study of the opportunities and priorities for isotope research and production…result(ing) in a Long-Range Strategic Plan for the Office of Science for Nuclear Physics
- Articulate the progress has been made since the last NSACI sub-committee published its recommendations, and the scientific and societal impacts of these accomplishments and ongoing activities
- Identify and prioritize the most compelling opportunities for the DOE Isotope Program to pursue over the next decade and articulate their impacts
- Indicate the resources needed in the timeframe 2016-25 to increase the domestic availability of isotopes appropriate to the DOE Isotope Program portfolio and deemed to be critical to the Nation.

A copy of the full charge letter is provided in Appendix 1; this report provides our response.

The NSACI subcommittee membership (listed in Appendix 2) was again chosen to have broad representation from the research, industrial, and homeland security communities. In addition, one third of the members were also on the 2009 NSACI, providing important points of reference for our evaluation of the progress of IDPRA in meeting the goals set in 2009. A total of three meetings were held by the subcommittee to gather information and develop a consensus on our responses to our charge. The agendas of the three meetings are provided in Appendix 3. The subcommittee heard presentations and/or received written input from a large number of federal institutions, professional societies, industry trade groups, and individual experts who were contacted for input (listings of the organizations contacted are provided in Appendices 4-6).

The Strategic Plan presented here builds on the original Strategic Plan developed by the 2009 NSACI subcommittee [NSACI09A], and on the thoughtful realization of the critical points of that plan by the Office of Nuclear Physics.

Chapter 2: The DOE Isotope Program

2.A. Origins and History

The history of the practical use of isotopes is almost as long as the history of the discovery of radioactivity and the development of accelerators that could induce nuclear reactions to create them. (See Sidebar 1 for a brief explanation of isotopes.) That history is also deeply entwined with the history of a number of laboratories that are, today, part of the DOE National Laboratory system. For example, nuclear medicine was one of the earliest applications of isotopes. Science historians identify its birth as occurring somewhere between 1934 (when artificial radioactivity was first discovered) and 1946 (when radionuclides were first produced for medical use by the Oak Ridge National Laboratory) [SNM15]. Many identify John Lawrence as the father of nuclear medicine. The brother of E. O. Lawrence, the inventor of the cyclotron, John took a leave of absence from the Yale Medical School in 1935 to visit his brother at the new radiation laboratory he had founded (now known as the Lawrence Berkeley National Laboratory or LBNL) in Berkeley, California. John started the Donner Laboratory at LBNL in about 1936, and made the first application of an artificial radionuclide in patients when he used ^{32}P to treat leukemia.

The DOE National Laboratory system, and its predecessors under the Atomic Energy Commission (AEC) and the Energy Research and Development Administration (ERDA), has played a major role both in the development of many of the applications of isotopes and in the development of the technology necessary to produce the required isotopes in useful quantities and purity (see the two 2009 NSACI reports [NSACI09, NSACI09A], and particularly Chapter 2 of the second of these reports for details). The formal support for this effort began with the 1954 Atomic Energy Act, which directed the AEC to ensure the continued conduct of research and development and training activities in a number of areas including nuclear processes and the utilization of radioactive material for medical, biological, and health purposes. That effort has continued through the transfer of the laboratories to ERDA in 1974, and the subsequent transfer to DOE in 1977, and it continues within DOE to this day.

Today isotopes have many applications in areas such as biology, medicine, pharmaceuticals, the physical sciences, engineering, and national security. Sidebar 2 below identifies highlights among these applications. Further examples and details are provided in Chapter 3 of this report, and in a number of the sidebars in both this report and the two reports of the 2009 NSACI subcommittee [NSACI09, NSACI09A]. The scale of the applications can be gauged from the 2009 study [ITS09] by the U.S. International Trade Commission of isotope shipments in the U.S. in 2007 that placed the total value at $3 billion.

In 2009, the Isotope Program was transferred within the DOE from the Office of Nuclear Energy to the Office of Science's Office of Nuclear Physics (DOE-NP) and formally named the Isotope Development and Production for Research and Applications Program (IDPRA). Among the actions taken in preparation for that transfer, DOE-NP requested that the Nuclear Science Advisory Committee (NSAC) establish the NSAC Isotope (NSACI) subcommittee to advise it on specific questions concerning the Isotope Program. NSACI was asked: to identify and prioritize the compelling research opportunities using isotopes; and to study the opportunities and priorities

Sidebar 1: What is an Isotope?

Atoms are composed of an extraordinarily small, positively charged atomic nucleus surrounded by a cloud of light, negatively charged electrons that occupy most of the volume of the atom and characterize how it interacts with other atoms. The atomic nucleus is made up of relatively heavy (~2000 × the mass of the electron), positively charged protons and similarly heavy neutrons, which have no electrical charge. The number of protons (Z) in the nucleus determines the number of electrons, and thus the chemical element of the atom. However, Nature allows nuclei with many possible neutron numbers (N) for the same proton number; these differing arrangements are called the isotopes of the element. To date, 118 elements have been discovered or reported discovered, with 4 still to be confirmed. Ninety of these occur naturally in at least trace amounts, while traces of the others can be found in unusual circumstances or are man-made [EM12]. We anticipate that there are about 7000 isotopes that live longer than a few nanoseconds, but to date only about half of them have been identified.

Some of these isotopes are stable. For example, carbon, which has 6 protons, has two stable isotopes, ^{12}C and ^{13}C (sometimes denoted C-12 and C-13) where the C identifies the element as carbon and the superscripts 12 and 13 designate the total number of protons and neutrons, and, to an accuracy of about 1%, give the mass of the atom in atomic mass units. In nature, about 98.9% of all carbon is ^{12}C and 1.1% is ^{13}C. The difference in abundances is due to substantial differences in the rates of nuclear reactions between isotopes when the elements are created in stars and stellar explosions. Since they behave very similarly chemically, but can be separated physically (either directly using centrifuges, or by taking advantage of the fact that moving ions with differing charge to mass ratios bend differently in a magnetic field) ^{13}C is very useful in biology, for example for nutrition studies. There are a total of 13 known isotopes of carbon, with half-lives for nuclear decay between 5715 years (for ^{14}C, which is used in radioactive carbon dating), to 20 minutes for ^{11}C (used in positron emission tomography for medical diagnosis) to 0.009 s for ^{22}C.

While in most cases, only the ground state of a nucleus lives long enough to be useful for applications, there are some instances where an excited state has particularly useful properties. These states are known as “isomers” and are designated with an “m” for metastable. An especially useful isomer occurs in an isotope of technetium with mass 99. This isomer, ^{99m}Tc, is used in about 14 million medical procedures a year in the United States.

Useful quantities of unstable isotopes typically must be artificially created by man via nuclear reactions using particle accelerators or nuclear reactors (See Chapter 6.B and 6.C). In most cases, stable isotopes can be separated out of naturally occurring materials (See Chapter 6.A). However if a stable isotope, such as ^{3}He (with an abundance of 0.0001%), is sufficiently rare, it too must be created through man-made nuclear reactions.

for ensuring a robust national program in isotope production and development, and to recommend a long-term strategic plan that will provide a framework for a coordinated implementation of IDPRA.

Sidebar 2: A Century of Benefits of Isotopes – Understanding our World, Securing our Safety and Environment, Enhancing our Industries, and Improving our Health and Quality of Life.

For more than a century, we have sought to identify, purify, produce or create new isotopes for a multitude of applications. New elements have taught us the fundamentals of our physical laws and about the history of the universe. A variety of radiotracers and stable isotopes are used to label important molecules in living cells and in biochemical reactions to understand their metabolism and biology. Isotopes are essential to modern industries ranging from powering spacecraft, to enabling oil fracking, to calibrating atomic clocks. Diagnostic medical imaging with radioisotopes is used to detect small cancers before they metastasize, to characterize a cancer's growth rates and its response to treatment, and to predict outcomes for patients. Nearly 20 million scans are done annually in the United States. Positron emitters can precisely determine the volume of the cancer in three dimensions. Heart function can be measured to allow appropriate therapy and prognosis. Neurodegenerative and psychiatric disorders can be studied. Other, therapeutic isotopes are employed to treat cancers, either by direct infusion of the element or after attachment to a targeting vehicle, such as a monoclonal antibody or peptide. Bone pain from cancer metastasis can be minimized. Thyroid cancers, neuroendocrine tumors, leukemia and lymphoma can be reduced in volume by use of radioisotopes. Radioisotopes also were the basis of external beam radiation therapy, used in half of all patients with cancer, such as for the most frequent tumors of the breast, prostate, lung. Radioactive seeds can be implanted directly into tumors to shrink them. Finally radioisotopes have been essential components of our energy sources and national security.

Application	**Selected Isotope Examples**	**Selected Important Uses**
Diagnostic imaging of human disease	*Gamma imaging:* ^{201}Tl, ^{99m}Tc, ^{111}In, ^{131}I, ^{133}Xe	Measuring cardiac and renal function, cardiac and lung perfusion; identification of cancers and inflammation; for cancer diagnosis, prognosis and treatment monitoring.
	Positron (PET) imaging: ^{18}F, ^{124}I, ^{68}Ga, ^{89}Zr, ^{64}Cu, ^{86}Y, ^{11}C, ^{15}O, ^{82}Sr/^{82}Rb	Neuroimaging for Alzheimer's disease and epilepsy. Cancer detection and treatment response quantification.
Therapy of human disease	*Beta-emitters:* ^{131}I, ^{90}Y, ^{89}Sr, ^{177}Lu, $^{186/188}$Re, ^{90}Y, ^{153}Sm	Therapy using ^{131}I, ^{90}Y, ^{177}Lu, and ^{188}Re; pain palliation using ^{89}Sr, ^{186}Re & ^{153}Sm
	Alpha-emitters: ^{223}Ra, ^{225}Ac, ^{211}At, ^{213}Bi, ^{212}Pb/^{212}Bi	Therapeutic applications, including prostate cancer with ^{223}Ra, leukemia with ^{225}Ac and ^{213}Bi, and glioma with ^{211}At. ^{212}Pb used for treatment of melanoma, breast cancer, and ovarian cancer
Fixed therapeutic sources	*External beams:* ^{60}Co	High energy γ-rays produced for external beam radiotherapy.
	Internal brachytherapy: ^{192}Ir, ^{125}I	High energy beta particles produced from seed or wire implanted into patient.
Biological, biochemical, and chemical research tracers	^{3}H, ^{32}P, ^{33}P, ^{125}I, ^{35}S, ^{51}Cr, ^{75}Se, ^{14}C	Tracer isotopes are incorporated into DNA, RNA, proteins and lipids to study their functions and metabolism in vitro and in vivo; ^{51}Cr is used to measure viability of cells.
Power sources	^{238}Pu, ^{90}Sr, ^{244}Cm	Used for remote, long-lived devices such as spacecraft.
Nuclear and particle physics, chemistry and engineering	^{237}Np, ^{239}Pu, ^{244}Pu, ^{243}Am, ^{248}Cm, ^{249}Bk, ^{249}Cf, ^{225}Ra, ^{48}Ca	Creating heaviest elements in atomic table; understanding matter and its forces.
Fission and reactor function	^{233}U, ^{235}U, ^{238}Pu	Nuclear reactor cores, breeder reactors, and nuclear weapons
Environment, security and safety	*Sensors, tracers and detectors:* ^{241}Am, ^{137}Cs, ^{252}Cf, ^{6}Li, ^{14}C, ^{3}He, ^{75}Se, ^{133}Cs, ^{65}Ni	Smoke detectors, oil exploration and explosives detectors. ^{14}C is used to date biologic materials and life forms.
	Coolants: ^{7}Li, ^{10}B	Used for reactors
Stable Isotopes	^{13}C, ^{15}N, ^{18}O	Proteomics and analytical studies. Target for ^{18}F production. Used for quantitation of metabolism.

2.B. Today (2009 to Present)

The two 2009 NSACI reports [NSACI09, NSACI09A] set the course for IDPRA, with recommendations on: how it should be organized and conduct business; investments that needed to be made in development of a highly-trained workforce for the future; investments that needed to be made in production capability; and compelling research opportunities. It is clear that the Isotope Program has been pursuing these recommendations vigorously in the intervening half dozen years, and many changes have occurred in the program since its move to the Office of Nuclear Physics and since the 2009 NSACI reports. The details and our evaluation of them are discussed in detail in Chapter 9 of this report. Broadly, we are impressed with the care and thoroughness with which the recommendations have been implemented; the result is an outstanding program that is making essential contributions to the Nation.

The primary DOE facilities currently used to produce isotopes are shown in Figure 1. IDPRA has responsibilities for isotope activities at five national laboratories in conjunction with various DOE offices. The Brookhaven Linac Isotope Producer (BLIP) at Brookhaven National Laboratory uses the linac injector of a DOE-NP facility, the Relativistic Heavy Ion Collider, to provide up to 200 MeV proton beams of up to 105 μA in both parasitic and dedicated running modes. At Los Alamos National Laboratory, the Isotope Production Facility (IPF) at the Los Alamos Neutron Science Center (LANSCE) provides 100 MeV 400 μA proton beams, again in both parasitic and dedicated running modes. LANSCE's primary support comes from DOE/NNSA. Proton beams of the energies available at BLIP and IPF are not available elsewhere in the United States for isotope production. The host facilities (RHIC and LANCE) are primarily funded to support other missions; isotope production is a secondary mission.

At Oak Ridge National Laboratory, the 85 MW High Flux Isotope Reactor (HFIR) is operated by the DOE-Office of Basic Energy Sciences mainly for neutron scattering research, materials research, and heavy element production, but it also produces isotopes for IDPRA through a user fee funding program. Oak Ridge also houses the Isotope Business Office (part of the National Isotope Development Center, NIDC), Materials Laboratories, and the inventory of enriched stable isotopes, and IDPRA has stewardship responsibility for the processing capabilities there. BLIP, IPF, and HFIR all have extensive radiochemical laboratories for processing and packaging radioisotopes and the required shipping infrastructure for transporting them safely and efficiently to customers.

Three other DOE facilities provide isotopes through the DOE Isotopes Program. At Idaho National Laboratory, the Advanced Test Reactor (ATR), operated by the DOE-Naval Reactor program, is used for ^{60}Co production under a user fee funding arrangement. Studies are underway to investigate the use of ATR for production of other isotopes. The Pacific Northwest National Laboratory (PNNL) has extensive radiochemical laboratory facilities (Radiochemical Processing Laboratory, or RPL) which contribute to isotope separation through user fee funding. Finally, the Savannah River Site and Savannah River National Laboratory provide ^{3}He obtained from the decay of tritium stocks from the dismantlement and maintenance of nuclear weapons.

Special considerations have led to the responsibility for certain isotopes to be assigned to other areas of DOE. These include weapons material such as tritium, enriched uranium, and plutonium. As discussed in Sidebar 9, DOE/NNSA has the lead responsibility for ^{99}Mo, in large

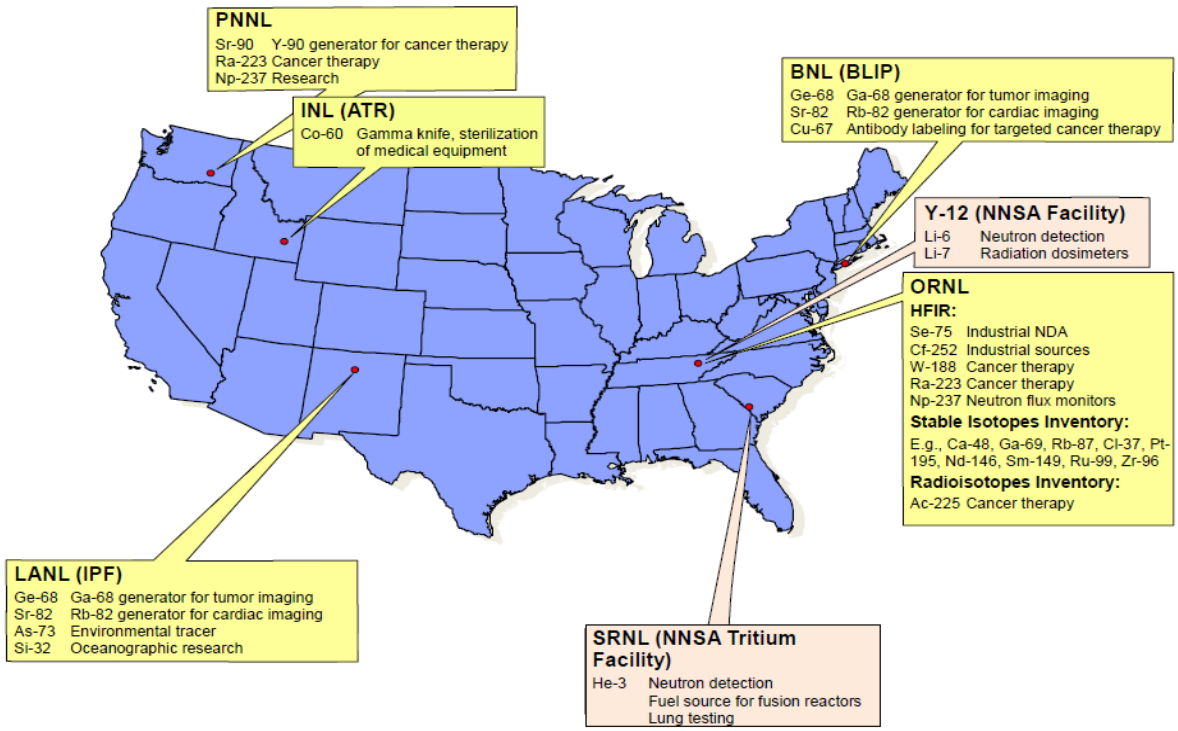

Figure 1: The Network of DOE Isotope Production Sites and examples of isotopes produced or distributed from each site.

part due to their non-proliferation responsibilities to reduce or eliminate the use of highly-enriched uranium in the production cycle. ^{6}Li and ^{7}Li (obtained from Y-12 at Oak Ridge National Laboratory by DOE/NNSA from the reprocessing of material from the dismantlement of nuclear weapons) are processed, distributed, and sold through the DOE Isotopes Program. The Office of Nuclear Energy handles production of ^{238}Pu used for NASA deep space power sources.

The Isotope Program is developing links to a number of university facilities in an effort to interface with them in order to augment the capabilities of the national laboratories and to further enhance both R&D activities involving the universities and the workforce training activities they carry out (see Chapter 9). One of the university facilities, the 10 MW Missouri University Research Reactor (MURR), has a long history and a major program in isotope production. In 2014 MURR supplied 35 different isotopes and made over 1100 shipments to a variety of national and international customers. Recognizing these broad capabilities and the need to ensure multiple isotope production streams, the Isotope Program and MURR are in discussions about MURR supplying select isotopes in cooperation with the Isotope Program.

A video providing an overview of the Isotope Program along with an introduction to the important role isotopes play in science and society is available on YouTube:
https://www.youtube.com/watch?v=44mbZDKGb80

The FY2015 appropriated federal budget for the Isotope Program is $19.84M and revenue from sales is anticipated to be ~$36M; the revenue is used to pay for the production costs of the isotopes sold, and appropriated funds provide for mission readiness and modest R&D funding. Chapter 10 discusses budgets we consider appropriate in response to our charge to "indicate what resources would be needed in the timeframe 2016-2025 for the program to increase the domestic availability of isotopes appropriate to the DOE Isotope Program portfolio and deemed to be critical for the Nation". We also discuss the impacts of a constant effort budget.

Chapter 3: Uses of Isotopes

Isotopes touch the lives of almost every citizen. They are essential elements in areas ranging from medical treatments to basic research and national security. Examples of their many applications are identified in Sidebar 2. In this chapter, we review the uses of isotopes in three broad categories: Biology, Medicine and Pharmaceuticals; Physical Sciences and Engineering; and National Security and Applications. Then, in Chapter 4, we identify research opportunities that are expected to further expand the impact of isotopes on our lives.

3.A: Biology, Medicine, and Pharmaceuticals

Radioisotopes are used routinely in many aspects of biology, medicine and pharmaceuticals. A primary use of radioisotopes in this area is in the safe and effective diagnosis, assessment and treatment of disease in the field of nuclear medicine.

Radioisotopes are generally used to 'label' a radiopharmaceutical. The overall chemical structure of the radiopharmaceutical determines its biological properties (e.g. targeting), while the radioisotope determines imaging or therapeutic properties. As diagnostic agents, isotopes emit radiation that allows specialists to image the extent of a disease process in the body, based on cellular function and physiology. This provides doctors with a better understanding of the diseased tissue than is available through other diagnostic procedures, which may only capture anatomical information. As therapeutic agents, radioisotopes can deliver highly targeted radiation to target tissue while sparing side effects to normal tissues.

^{18}F is a commonly used isotope for medical imaging, illustrated by the success of [^{18}F]fluorodeoxyglucose (FDG), a sugar analogue used in imaging during diagnosis and follow up of many malignant tumors as shown in Figure 2. For cancer imaging, this radio-pharmaceutical exploits the high glucose uptake by tumors to visualize metabolic activity before and after treatment.

Current Uses of Isotopes for Imaging

There are three major types of nuclear medicine imaging: planar scintigraphy; single photon emission computed tomography (SPECT); and positron emission tomography (PET).

Planar Scintigraphy and SPECT Imaging: Both planar scintigraphy and SPECT imaging use gamma emission from radiopharmaceuticals to image or determine organ function in patients. Planar scintigraphy results in two-dimensional images while SPECT provides three-dimensional information. These are used in about 14 million medical procedures each year in the United States. More than 85% of SPECT imaging uses ^{99m}Tc, which is derived from ^{99}Mo/^{99m}Tc generators in which 66 hour half-life ^{99}Mo decays into ^{99m}Tc.

The five major ^{99}Mo producers have been increasing their production capacity since the 2009-2010 period when two major reactors required unexpected maintenance. These reactor shutdowns led to shortages of ^{99}Mo and ^{99m}Tc for clinical use. Even though ^{99}Mo production capacity has increased since then, the NRU reactor in Canada is expected to stop routine production of ^{99}Mo in October, 2016 (it may be available for emergency use until March 2018).

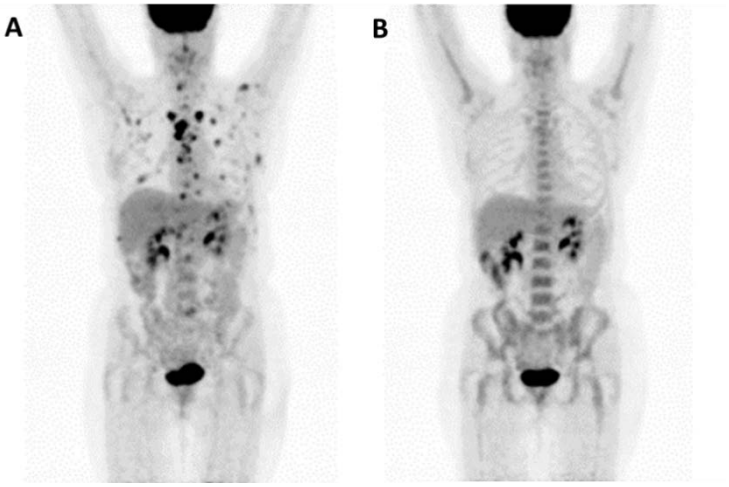

Figure 2: [^{18}F]fluorodeoxyglucose scan of a woman diagnosed with T-cell lymphoma. A. The image at diagnosis shows uptake in extensive disease sites along with normal signal in the brain and bladder, and B. The image following 4 months of chemotherapy shows the dramatic decrease in signal in the cancer sites indicating that this patient is responding well to therapy. (*Image courtesy of Dr. Jonathan McConathy, Washington University in St. Louis.)*

This loss of capacity is expected to be covered primarily by a large capacity increase from ANSTO in Australia and production capacity increase from the other three major ^{99}Mo producers. The ^{99}Mo situation is summarized Sidebar 9 in Chapter 5; as noted there, it is not the responsibility of IDPRA, but rather of NNSA, so it is outside the scope of this NSACI report. Other SPECT radiopharmaceuticals include the radioisotopes ^{131}I, ^{133}Xe, ^{111}In, and ^{125}I, which is used for laboratory analyses. Most radioisotopes used in SPECT are commercially available and produced by research reactors or manufacturer-owned medium energy cyclotrons

PET Imaging: PET isotopes emit positrons, the antiparticle of electrons. When a positron meets an electron, they annihilate producing to two back-to-back gamma rays, which leave the body. By detecting these gamma rays, the location of the activity in the body can be determined and an image can be reconstructed. Due to its high sensitivity and resolution, PET is growing rapidly as an imaging technology.

In addition to the ^{18}F used for ^{18}F [FDG], other PET radioisotopes include ^{82}Rb, ^{11}C, and ^{13}N. These are typically produced in small PET cyclotrons operated locally by hospitals and nuclear pharmacies. The nuclear pharmacies provide a decentralized distribution network that typically supplies a small geographical area due to the short half-lives of these radioisotopes. This is in contrast to other radiopharmaceuticals, which are distributed centrally by radiopharmaceutical manufacturers.

The Isotope Program plays a major role in the production and distribution of ^{82}Sr for use in production of ^{82}Rb generators. This is discussed in Sidebar 11 and in Chapter 6 of this report. The program also plays an important role in the production of ^{68}Ge for the use in ^{68}Ga generators, currently being used under Investigational New Drugs (INDs) in the U.S and discussed in chapter 4A. Prior to 2014, the Isotope Program had been a larger producer of ^{68}Ge for use in ^{68}Ga generators, calibration, and transmission sources. After a petition by

Mallinckrodt Pharmaceuticals, the Isotope Program exited the market for ^{68}Ge sales used to produce calibration and transmission sources.

Therapeutic Uses of Isotopes

Emission Characteristics: Different radioisotopes emit a variety of different forms of radiation characterized by different wavelengths, particle types, energies, and ranges of penetration inside human tissue. These differences are key for the appropriate choice of radioisotope in different therapeutic settings. Individual cancer cells are typically 15-30 microns in diameter whereas tumor nodules may range from a few millimeters to several centimeters. The choice of radioisotope for therapy should be matched to the target geometry of the cancer, which can range from individual cancer cells as occurs in leukemia, to micrometastatic deposits of hundreds to a few thousand cells, to large, centimeter scale bulky masses, such as in a lymphoma or a solid tumor. Beta particles, like those emitted from ^{131}I**,** ^{90}Y and ^{177}Lu, typically have ranges of 1 millimeter to several millimeters (Table 1). In contrast, alpha-emitters, such as ^{213}Bi, ^{225}Ac, ^{223}Ra, and ^{211}At, have ranges in the tens of microns. As a consequence, initial attempts to use alpha particles have focused on leukemias and small micrometastatic deposits of cancer cells, while the uses of beta-emitters have generally been directed to the treatment of larger, bulkier cancers because the particle travels farther.

Table 1: Characteristics of Therapeutic Isotopes

Form of decay	**Energies (keV)**	**Range (μm)**	**Examples in use**
Beta particle	200-2000	300-10,000	^{131}I, ^{177}Lu, ^{90}Y
Alpha particle	5000-11,000	40-80	^{223}Ra, ^{213}Bi, ^{225}Ac, ^{211}At
Auger electron	0.02-0.5	0.001-1	^{125}I, ^{123}I

Another feature of radioactive emissions is their linear energy transfer (LET). Alpha particles have far higher energies of decay (up to 10 million electron volts), but travel a short distance (microns), yielding a high LET radiation, which means a large amount of energy is deposited along the path length. A consequence of this deposition is that it may only require a single alpha particle passing through the nucleus of a cancer cell to kill that cell, making alpha particle therapy extremely potent and effective. Beta decays provide lower doses of energy over a longer path length and therefore generally allow the radiotherapy to kill bulkier tumors, as well as cancer cells within the tumor that may not have been targeted directly by the radioisotope. The longer-range radiation can also have effects on non-target tissue, whereas alpha-emitters tend to spare such tissues more effectively than beta particles.

The most specific form of radiation for therapeutic use is the Auger electron, in which an atom in an excited state undergoes a transition to a lower state by the emission of a bound (Auger) electron rather than by the emission of an x-ray. Auger electrons have path lengths ranging from nanometers to a micron. However, due to this narrow range, the radioisotope must be inside of the cell, and often inside of the nucleus, to best achieve its therapeutic effect. On the other hand, if the Auger-emitter is targeted appropriately, there is little chance of this type of radiation damaging normal tissues.

Targeting and Delivery of Radioisotopes to Cancers: The more selectively a radioisotope can be delivered to the target cancer cell, the safer the treatment. While all radiopharmaceuticals and radiation therapies rely to some degree on selective targeting, most also require the addition of a ligand or carrier molecule to deliver the isotope to its intended site within the patient. There are four general classes of radiation therapies (Table 2).

Table 2: Types of radiotherapy approved or in development in clinical trials

Type of therapy	**Typical Isotope**	**Radiation form**	**Diseases treated**
External beam irradiation	^{60}Co	X-ray, proton, or gamma ray from source.	Breast, prostate, lung, ovary, colon cancer, sarcomas, uterine, lymphomas, and many others.
Systemically administered isotope	^{131}I, ^{223}Ra, ^{89}Sr, ^{153}Sm	Free radio-halogen or radio-metal, or small molecule ligand, targets cancer tissue.	Thyroid cancer, prostate or breast cancer metastases, neuroendocrine tumors, among others.
Systemic Radioimmunotherapy	^{131}I, ^{90}Y, ^{211}At, ^{225}Ac, ^{213}Bi	Isotope labeled to antibody or peptide	Lymphoma, leukemia, glioblastoma, other solid tumors.
Brachytherapy	^{192}Ir, ^{103}Pd	Sealed source in seed or wire for implantation.	Prostate, breast, cervical, endometrial, head and neck, esophageal, lung cancers; sarcomas.

First, external beam gamma irradiation can be directed from an external source, such as from ^{60}Co, to sites within the body by precise focusing and modulation of dose and angle of penetration. Because of the long range of the gamma rays, efficacy and toxicity depends on the ability to guide the beam to the tumor while minimizing damage to normal tissues.

Radiotherapy may also be administered systemically to achieve selective cancer cell killing. ^{131}I is an excellent example of a radioisotope that specifically targets thyroid cancer due to the metabolism of the thyroid carcinoma cells. Injection of radioiodine results in accumulation of the isotope selectively within the cancer leading to specific killing of that cancer. Excretion routes of the non-targeted isotope, such as in the gastrointestinal tract, can be blocked pharmacologically to stop the uptake in normal tissues. Other isotopes such as ^{153}Sm and ^{89}Sr selectively accumulate in the bone or near bone marrow metastasis and can be effective at reducing pain of bone metastasis.

Others can prolong life, as in the case of ^{223}Ra treatment of patients with metastatic prostate cancer. ^{223}Ra dichloride was the first FDA approved alpha-emitting radiopharmaceutical. This drug combines high potency, high LET, and low toxicity as its key features (see Sidebar 3). Various means have been developed to direct radioisotopes to cancers when the elemental form does not reach the target tissues by itself. This includes the use of small molecule ligands, such as *meta*-iodobenzylguanidine labeled with ^{131}I to treat pheochromocytoma, or attachment of

^{177}Lu, ^{90}Y, or ^{213}Bi to a peptide such as tyr-octreotide to treat neuroendocrine tumors. Selective delivery of the isotope can also be achieved by use of a monoclonal antibody specific for a cell surface protein, such as with antibodies to CD20 to treat lymphomas. The use of monoclonal antibodies to direct radioisotopes to cancer cells (known as *radioimmunotherapy*) has enormous promise and versatility because nearly every cancer cell expresses antigen epitopes to which a reactive monoclonal antibody can be produced. In addition, widely used and efficient methods are available to attach radiohalogens, such as iodine, chelated radiometals emitting beta particles, such as ^{90}Y and ^{177}Lu, or chelated alpha-emitters such as ^{225}Ac, ^{213}Bi, ^{211}At, to antibodies. Two antibody targeted radiopharmaceuticals initially were FDA approved for the diagnosis of colon cancer and prostate cancer. More recently, two therapeutic antibody-directed radioisotopes were FDA approved for the treatment of lymphoma. A large number of antibody targeted radiopharmaceuticals are in development for the treatment of leukemia, lymphoma, and a variety of solid tumors. Finally, it is possible to directly implant materials bearing radioisotopes in a sealed source that does not allow escape of the radioisotope into a tumor mass; this allows short-term or long-term irradiation just in that tumor site, largely sparing the surrounding normal tissues. This technique is known as *brachytherapy*. Isotopes frequently used for brachytherapy are ^{192}Ir, ^{103}Pd, or ^{125}I, which are contained in seeds or wires that can be implanted and removed when the treatment is finished.

Isotopes for Basic Research/Tracers

Radiotracers: With the development of the radiotracer technique by de Hevesy in the early part of the 20th century the opportunity to explore biological function in living systems became a reality. While the focus has been on the use of radiotracers in medicine for the last century, tracer techniques in other disciplines provide enormous opportunities to investigate complex chemical/biological systems.

Environmental Uses: ^{32}Si and ^{67}Cu can be used to better understand the interplay of microorganisms in the ocean and their role in controlling atmospheric CO_2.

The development of the use of radioactive ^{32}Si for the measurement of diatom production in the 1990s was revolutionary for oceanography. Its use allowed rapid and relatively uncomplicated measurements suitable for work with diatom cultures, but most importantly it was the only practical methodology to be used onboard oceanographic ships.

Diatoms, a group of aquatic microalgae, are responsible for fixing about 40% of atmospheric carbon (CO_2) through the process of photosynthesis. This carbon is incorporated into organic molecules (carbohydrates) and is then available for grazers and other organisms in the food chain. Because diatoms are the largest consumers of dissolved silicon (Si) in the oceans, they control the cycling of Si. When they die and sink, they contribute significantly to the downward flux of biogenic silica, nitrogen and carbon in most oceanic regions, being responsible for ~20% of the carbon fixed through photosynthesis on Earth [VA14].

Unfortunately, ^{32}Si is difficult to produce. ^{32}Si is two neutrons away from stability. The closest solid target material turns out to be KCl; both elements can be a source of ^{32}Si from high energy proton reactions inducing spallation of both of these target nuclei. However, the cross section (probability of producing ^{32}Si) is very low. In fact, after a year of irradiating a KCl target with

Sidebar 3: ^{223}Ra, an Alpha Therapy Success Story

Radium-223 (^{223}Ra), delivered as radium dichloride, is an isotope of radium with an 11.4-day half-life, compared to the more common ^{226}Ra, discovered by Marie and Pierre Curie, which has a 1601-year half-life. The principal use of ^{223}Ra, is as a therapeutic radiopharmaceutical to treat certain types of prostate cancer which has metastasized to the bone. The chemistry of ^{223}Ra is similar to calcium, allowing it to be taken up in bone by a similar mechanism, and it decays by the emission of an alpha particle that travels only a short distance in tissue, localizing the radiation dose.

^{223}Ra has been developed by the Norwegian company Algeta ASA, in a partnership with Bayer Healthcare, under the trade name Xofigo®, and is distributed as a solution containing ^{223}Ra dichloride (1000 kBq/ml) for intravenous injection. In May 2013, ^{223}Ra received approval by the U.S. Food and Drug Administration (FDA), and was the first FDA approved alpha-emitting radiopharmaceutical. It is used to treat castration-resistant prostate cancer (CRPC) with bone metastases in patients with symptomatic bone metastases and without known visceral disease. The recommended treatment regimen is six doses of 50 kBq/kg, repeated at 4-week intervals. Clinical investigations are ongoing to determine the safety and efficacy of increasing the administered dose to 100 kBq/kg. ^{223}Ra has also shown promising preliminary results with bone metastases resulting from breast cancer that no longer responds to endocrine therapy.

^{223}Ra is generally made artificially by exposing natural ^{226}Ra to neutrons to produce ^{227}Ra, which decays with a 42-minute half-life to ^{227}Ac. ^{227}Ac (half-life 21.8 years) then decays via ^{223}Th (half-life 18.7 days) to ^{223}Ra. This decay path makes it convenient to prepare ^{223}Ra by separating or "milking" it from an ^{227}Ac containing generator or "cow", similar to the ^{99}Mo cows widely used to prepare the medically used isotope ^{99m}Tc.

With the success of ^{223}Ra as a radiopharmaceutical treatment for metastatic prostate cancer, the public has been encouraged that radiation treatment with radioactive materials can be beneficial, and additionally does not have significant side effects compared to many chemotherapies. This will help to encourage the research development of other alpha-emitting radiopharmaceutical therapies for clinical use. One example is the radioimmunoconjugate of the alpha-emitting ^{225}Ac to the humanized monoclonal antibody lintuzumab which has been used to treat leukemia and is in clinical trials at Memorial Sloan Kettering Cancer Center [JU13].

Additionally ^{211}At labeled monoclonal antibody, 81C6, has been used in clinical trials at Duke University to treat patients with gliomas [ZA08], and clinical trials are being planned for ^{211}At trastuzemab to treat HER2 positive breast cancer neoplastic meningitis and ^{211}At labeled meta-astrobenzylguanidine (MABG) for children with neuroblastoma.

Increased use of alpha therapy for clinical trials and development of therapeutic radioisotope therapy as an alternative to chemotherapies requires increased production of these alpha radioisotopes including ^{225}Ac, ^{211}At, ^{213}Bi (also used for treatment of gliomas), and ^{212}Pb/^{212}Bi which is being investigated for various treatments including melanoma, breast cancer, and ovarian cancer [RO10]. Additionally there is increased opportunity for development of new alpha-emitting radioisotopes for potential commercialization. The Isotope Program is investigating efficient provision of all of these isotopes.

500 MeV protons with a nominal beam current of 100 μA, less than 250 μCi of ^{32}Si were produced. Fortunately, researchers need very little ^{32}Si because of the sensitivity of the measurements. Typical researchers require approximately 10 μCi/year. (The production of ^{32}Si is an example of a LANL/TRIUMF cooperation supported by the DOE Isotope Program.)

The physical and chemical properties of ^{67}Cu make it a promising radioisotope for use in targeted radiotherapy (see Chapter 4). These same properties also make it an important tracer for studying carbon dioxide (CO_2) sequestration by phytoplankton in the earth's oceans. Every year, the burning of fossil fuels contributes to the increasing levels of carbon dioxide (CO_2) in the Earth's atmosphere, which contributes to global warming. Global warming is already significantly affecting the ecology and functioning of many terrestrial and marine ecosystems.

The surface ocean plays a significant role in controlling atmospheric CO_2 levels, and is responsible for mitigating approximately 50% of the total anthrophogenic CO_2 released in the atmosphere since the industrial revolution. In turn, the CO_2 exchange between the upper ocean and the atmosphere is controlled by two pumps: the biological and the solubility pump. The solubility pump moderates CO_2 in the atmosphere through gas exchange and is mainly a temperature driven process (CO_2 is more soluble in cold water), while the biological pump is controlled by the production of microscopic algae, phytoplankton, in the surface ocean. Phytoplankton are single-celled organisms that have inhabited the earth's oceans for billions of years. Similar to plants, phytoplankton use photosynthesis to convert CO_2 into simple sugars. The higher the productivity of phytoplankton in the surface ocean, the more CO_2 is pulled from the atmosphere and the greater the potential of exporting this organic carbon to the deep ocean as sinking particles. Today's atmospheric CO_2 level is around ~400 parts per million (ppm). Without marine phytoplankton, the Earth's atmospheric CO_2 has been estimated to be > 700ppm. At maximum efficiency atmospheric CO_2 could be as low as ~ 300 ppm.

In the last 20 years, we have learned that phytoplankton productivity in 30% of the global ocean is limited by the supply of the micronutrient, iron (Fe). To understand fully the impact of Fe limitation on the growth and cellular physiology of marine phytoplankton, it is critical to determine the metabolic processes that control uptake and utilization of Fe by these organisms. In the last 10 years, Canadian scientists have used Cu radioisotopes (^{64}Cu and ^{67}Cu) in the field (ocean) and the laboratory to demonstrate that Cu plays an essential role in the ability of phytoplankton to acquire the minute concentrations of dissolved Fe in surface waters. The research continues to elucidate the role of Cu in the physiology of Fe limited phytoplankton, which has the potential to make significant progress toward understanding what controls phytoplankton productivity in 30% of the global ocean (the Fe-limited regions), and ultimately what controls the global carbon cycle [MA14].

3.B: Physical Sciences and Engineering

Replacing one isotope of an element with another can result in unique responses under various probes in solids, liquids, and gases. This may simply be due to the mass difference of the atomic nucleus, which couples to electronic degrees of freedom; the spin of the nucleus and, therefore, its response to magnetism; or the nuclear structure, which can undergo large variations even with a single neutron addition. This unique behavior allows scientists to directly examine the molecular environment in the sites where the isotopes are placed, lending itself to a plethora of

useful applications. Thus isotopes have found fundamental and technological applications in almost all branches of sciences and engineering. Examples range from the study of the very small (elementary particles) to the very large (planets and exploding stars), and from the study of the very old (geology) to the very new (nanoscience). For example, isotopes are intimately involved in processes for energy production, industrial diagnostic methods, archeology, geology (terrestrial and extra- terrestrial), ecology (carbon and nitrogen cycle), and astronomical science. Isotopes enable the search for new sources of energy, help manage the natural resources like water and forests, and provide for home and food safety.

While the discovery of isotopes is about 100 years old, today about 250 stable isotopes of the 90 naturally occurring elements are known. The number of natural and artificial radioactive isotopes exceeds 3200, and keeps growing every year. The origin of our understanding of the existence of isotopes dates to F. Soddy's discovery [FO10] in 1910 that lead (Pb) obtained by decay of uranium and thorium differed in mass from most lead; this was considered a peculiarity of radioactive materials. In 1913 Soddy [SO13], and independently Fajan [FA13], developed a displacement law, which explained the change in mass and how that affected the place in the periodic table after α-decay or β-decay occurs and its implications on the formation of isotopes.

Nuclear Physics

It is perhaps obvious that isotopes are essential tools in basic research across all of nuclear physics. Indeed, one of the central thrusts expressed in the DOE/NSF Nuclear Science Advisory Committee Long Range Plan for nuclear physics [NSAC07] is to understand how the properties of the nucleus change as the ratio of the number of neutrons to number of protons varies. This research requires experiments with a variety of isotopic targets and beams. It compellingly leads to the study of ever rarer and rarer isotopes that are far in neutron number from the stable isotopes. The Department of Energy is constructing a major new science user facility, the Facility for Rare Isotope Beams (FRIB) at Michigan State University, to provide world leading capabilities for this science. At other frontiers of nuclear science, many of the most important experiments depend on the reliable and affordable availability of isotopes. In understanding the nucleon at the fundamental quark and gluon level, targets and beams of ^{2}H and ^{3}He allow access to the neutron. In looking beyond the Standard Model with tests of fundamental symmetries, the important experiments rely on a number of key isotopes.

Specifically, enriched stable isotopes are needed for use as target materials and for accelerated beams at various laboratories that produce both stable and radioactive beams needed to study the structure of nuclei. For example, ^{48}Ca is a neutron-rich isotope that is commonly used as a beam at various nuclear physics laboratories to study the properties of exotic nuclei far from stability. Scientists are also creating new elements in the periodic table and establishing their unique chemical attributes using this and similar isotopes. These latter experiments require actinide targets, including various isotopes of uranium, neptunium, plutonium, americium, curium, californium and berkelium. Research in actinide chemistry also is important for environmental studies of the migration of plutonium and other actinides and the effective disposal of nuclear waste. Production of the heaviest elements using actinide targets is further highlighted in Sidebar 4 below.

Investigation of the structure and reactions of atomic nuclei: The Argonne Tandem Linac Accelerator System (ATLAS) is a DOE-funded scientific user facility for the investigation of the

structure and reactions of atomic nuclei in the vicinity of the Coulomb barrier. A major advance in rare-isotope capabilities at ATLAS is the Californium Rare Ion Breeder Upgrade (CARIBU). Rare isotopes are obtained from a one-Curie ^{252}Cf fission source located in a large gas catcher, from which they are extracted and accelerated in ATLAS. CARIBU will provide accelerated neutron-rich beams with intensities up to 7×10^5 particles/s, and will offer unique capabilities for a few hundred isotopes, many of which cannot be extracted readily from existing Isotope Separator On Line (ISOL) type sources. In addition, it will make these accelerated beams available at energies up to 10-12 MeV/nucleon, which are difficult to reach at other facilities. Replacement ^{252}Cf sources of about 1 Ci will be required roughly every 1½ - 5 years for CARIBU to fulfill its scientific promise.

The National Science Foundation (NSF) operates the National Superconducting Cyclotron Laboratory, NSCL, which is one of the Nation's major science user facilities in nuclear structure and astrophysics. The primary research mission is to understand the nature of the nuclear force, structure of atomic nuclei, and the origin and evolution of chemical elements in the universe using beams of rare isotopes. The research relies primarily on isotopes not normally found in nature but produced at the facility. These rare isotopes are produced in-flight from beams of stable isotopes of elements ranging from helium up to uranium. The research relies on sources of separated stable isotopes, including ^{48}Ca, ^{86}Kr and ^{82}Se among others.

The next major science user facility in the field will be the DOE Office of Nuclear Physics funded Facility for Rare Isotope Beams, FRIB, at the Michigan State University. It will be the world's most powerful rare isotope beam facility, making nearly 80% of the isotopes predicted to exist for elements up to uranium. The production scheme also requires a supply of separated stable isotopes. Access to this wide range of isotopes will provide unprecedented opportunities to study the origin and stability of nuclear matter. With its ability to deliver the full elemental variety of reaccelerated beams, most of the reaction rates of astrophysical importance involving radioactive ions can be measured. It will be possible to carry out studies of a wide range of nuclei at the very limits of nuclear stability where specific aspects of the nuclear many-body problem can be explored. Separated isotopes of approximately 40 different elements will be required for optimal operation of FRIB.

Permanent electric dipole moment (EDM) of a quantum system: A very powerful probe of physics beyond the Standard Model of particles and interactions is to search for a *permanent electric dipole moment (EDM)* of a quantum system. The principles of quantum mechanics tell us that the interaction between an EDM and an applied electric field $\boldsymbol{E}$ is proportional to $\boldsymbol{S} \bullet \boldsymbol{E}$, where $\boldsymbol{S}$ is the spin of the object. This interaction energy changes sign if time is reversed (violation of time-reversal symmetry). In the Standard Model, the predicted effects that violate time reversal invariance are very weak. Indeed, the very fact that the observable universe is made of matter and not an approximately equal mix of matter and anti-matter is a compelling signal that time reversal must be violated at a much larger level than the Standard Model allows. Searches for permanent electric dipole moments are one of the most sensitive probes for this new physics. But these experiments require special isotopes. In the search for an electric dipole moment of the neutron, ^{3}He is required to align the spin of the neutrons and precisely determine the magnetic environment. Certain radioactive atoms possessing a large octupole deformation are expected to have greatly enhanced sensitivity to time-reversal violating forces in the nucleus. Both ^{225}Ra and ^{223}Rn show promise as potential high-sensitivity deformed nuclei. Currently,

Sidebar 4: Production of the Heaviest Elements using Actinide Targets

Where does the periodic table end? How many more elements are there? Are there any elements with longer half-lives and unique chemical or nuclear properties that are of practical use to humankind? These questions and more drive research into understanding the nuclear and chemical properties of the heaviest elements.

The production of the six heaviest elements, with atomic numbers of 113-118, has occurred using actinide target materials mainly produced in the U.S. High isotopic purity targets of ^{237}Np, ^{239,240,242,244}Pu, ^{243}Am, ^{248}Cm, ^{249}Bk and ^{249}Cf were used in this work, and these isotopes were sent to Dubna, Russia from various labs in the U.S. for this research. After confirming measurements, two new chemical elements took their place at the periodic table; element 114 was named Flerovium and element 116 was named Livermorium. This work is important because it expands our knowledge of the limits of nuclear and chemical stability.

In late 2004, it was proposed to perform the ^{48}Ca + ^{249}Bk experiment to attempt to synthesize element 117, but the ^{249}Bk target material was unavailable—it was no longer being produced and just discarded during the production of ^{252}Cf. In April 2008, a 250-day irradiation of Cm was begun at the HFIR for ^{252}Cf production and funding to separate the Bk was provided by LLNL and ORNL. After a 90-day cooling period in early 2009, Bk was separated and purified starting in April 2009. This material (See Figure 3) was sent to Dmitrovgrad, Russia for target fabrication followed by a 150-day irradiation in Dubna at the U-400 cyclotron with ^{48}Ca to produce element 117. Publication of the results of the experiment occurred in April 2010 – two years after the HFIR irradiation had begun. This work also highlights the co-operation between all collaborators to perform this experiment, given the 320-day half-life of ^{249}Bk, the international shipping needed, and the complex schedules of the accelerator and HFIR irradiation times required. Confirmation of this work by scientists at GSI using additional ^{249}Bk donated completely by the DOE Isotope Program prompted the American Physical Society to highlight it as one of the top-10 physics news stories in 2014 [APS15]. Future work includes in-beam experiments with a mixed ^{249,251}Cf target to extend production of the heaviest elements to the highest mass isotope of element 118. The production rate of elements 113-118 will be increased with upgrades at various accelerator facilities and the completion of the Super Heavy Element Factory in Dubna, dedicated to the production of the heaviest elements. New searches for elements beyond Z=118 will continue to be made. The DOE Isotope Program is working with this community to develop a strategy on how to provide the needed materials.

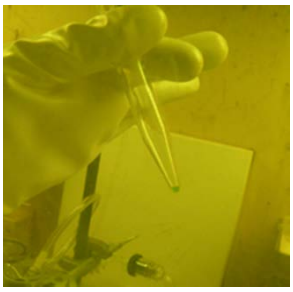

Figure 3: 22 mg of chemically purified ^{249}Bk (green solution in bottom of centrifuge cone) in a glove box at ORNL prior to shipment to Dmitrovgrad. *(image courtesy ORNL)*

It should be noted that continued production of actinide and transactinide isotopes with high isotopic purity will enable searches for new super heavy elements and stimulate the investigation of the chemical properties of the heaviest elements, in particular elements only sporadically studied because of availability like Es and Fm.

experiments using these nuclei are being planned or pursued at laboratories around the world, including Argonne National Laboratory (using ^{225}Ra extracted from a ^{229}Th source at ORNL) and TRIUMF in Canada (using a radioactive beam). The precision of the ^{225}Ra experiment is projected to be limited by the current isotope supply.

Neutrinoless Double Beta Decay: Neutrinos hold a special place in the standard model of particles and interactions. Of all the elementary quarks and leptons with spin ½, they are the only ones that are have no charge, and thus have the possibility of being their own antiparticle. We have only learned in the past two decades that neutrinos have mass, and since the limits on their masses are more than six orders of magnitude lower than the masses of the other elementary particles, it is quite possible that their mass is due to a different mechanism than that of the others, like quarks who acquire mass by coupling to the Higgs Boson recently discussed at the LHC. If neutrinos are their own antiparticle, then another mechanism for generating mass can plausibly explain this large difference. The most sensitive way to learn about this fundamental nature of the neutrino is to detect very rare nuclear decays, neutrino-less double beta decay where a nucleus such as ^{76}Ge decays to ^{76}Se by emitting only two electrons (similarly double beta decay of ^{136}Xe to ^{136}Ba , ^{48}Ca to ^{48}Ti, ^{130}Te to ^{130}Xe, and a few others). The observation of such a decay process would be the first demonstration that the lepton number is not conserved (since two electrons are created in the process without associated antineutrinos) and that the neutrino is indeed its own antiparticle.

However the probability of these decays is extremely small. Current research with detectors of about 50-100 kg of active material suggests that the lifetimes are greater than 10^{25} years (10^{15} times the age of the universe). Future experiments are expected to require a ton of active material. Since the relative abundance of the double-beta decaying isotope is usually small for the natural element (^{76}Ge, about 7%, ^{48}Ca, about 0.2%), providing ton scale quantities of separated isotope is a major challenge and a cost-driver for future experiments. However the scientific impact of the detection of these decays would be transformational.

Low temperature physics

An isotope that is broadly used in nuclear physics as well as low temperature physics is ^{3}He. As discussed in Chapter 3.B (and Sidebar 6), ^{3}He is also widely used as a neutron detector both for research and engineering and national security needs. Polarized ^{3}He is used as an effective polarized neutron in scattering experiments, e.g., at Jefferson Lab. There are plans to implement a polarized ^{3}He source at Brookhaven National Laboratory (BNL) to provide polarized neutron beams at the Relativistic Heavy Ion Collider (RHIC). As discussed above, ^{3}He is also a central element in the neutron EDM experiment planned for the Spallation Neutron Source (SNS) at Oak Ridge National Laboratory.

Many unusual phases of matter like superfluidity, superconductivity, and Bose-Einstein condensation occur at extremely low temperatures, which enable the study of subtle behaviors that are obscured by thermal motion at higher temperature. To reach a temperature below 0.3 K, a key technology is the ^{3}He - ^{4}He dilution refrigerator because it can operate continuously, provide a substantial cooling power at temperatures from around 1.0 K down to 0.010 K and below, and run uninterrupted for months. The ^{3}He - ^{4}He dilution refrigerator is also required for experiments that require temperatures as low as 0.001 K because it can be used to pre-cool the adiabatic demagnetization systems.

Climate Change and Environment

Mass differences between different isotopes cause sufficient change in bond strength and the vibrational characteristics of volatile compounds of H, C, N, and O to affect their heat of vaporization. Thus, time, temperature, and geographical variations of isotope ratio differences can be used as a tracer of climate change and help quantify the hydrogen, carbon, nitrogen, and oxygen cycle on earth. Isotopes are essential as calibration standards for these studies. For example, in *Paleoclimatology*, which studies climate change over the entire history of the Earth, oxygen isotope ratios [NA93] play an important role. Water with ^{16}O, $H_2{}^{16}O$, evaporates at a slightly faster rate than $H_2{}^{18}O$; this disparity increases at lower temperatures. Hence, the $^{18}O/^{16}O$ ratio provides a record of ancient water temperature. The measured heat capacity difference between $H_2{}^{18}O$ and $H_2{}^{16}O$ is 0.83 ± 0.12 J K^{-1} mol^{-1} for liquid water [NA93]. When global temperatures are lower, snow and rain from the evaporated water tends to be higher in ^{16}O, and the seawater left behind tends to be higher in ^{18}O. Marine organisms would then incorporate more ^{18}O into their skeletons and shells in warmer climates. Paleoclimatologists directly measure this ratio in the water molecules of ice cores or the limestone deposited from the calcite shells of microorganisms.

Nitrogen isotopic ratios also provide a powerful tool for evaluating processes within the nitrogen cycle and for reconstructing changes in the cycling of nitrogen through time. The biologically-mediated reduction reactions that convert nitrogen from nitrate (NO_3, +5 oxidation state) to nitrite (NO_2^{-1}, +3) to nitrous oxide (NO_2^{+1}), to nitrogen gas ($N_2{}^0$), and to ammonia (NH_3^{-3}) are faster for ^{14}N than for ^{15}N as a result of the higher vibrational frequency of bonding to ^{14}N than to ^{15}N. The nitrogen reduction process results in products that are ^{15}N -depleted relative to the substrate. If the substrate reservoir is either closed or has inputs and outputs that are slow relative to one of the reduction processes then the reservoir will become enriched in ^{15}N. Therefore, the stable isotope ratio of nitrogen can be a promising proxy for delineating the *eutrophication* in the environment, which is a process describing an increase in chemical nutrients — compounds containing nitrogen or phosphorus — in an ecosystem.

Astrophysics and planetary science

In astrophysics and planetary sciences, measurements of D/H, $^{13}C/^{12}C$, $^{15}N/^{14}N$, or $^{18}O/^{16}O$ of primitive solar system materials record evidence of chemical and physical processes involved in the formation of planetary bodies and provide a link to materials and processes in the molecular cloud that predated our solar system. Modern developments exploiting secondary-ion-mass-spectroscopy (nano-SIMS) methods have provided mineralogical and isotopic evidence of origins of stardust as composed of precursors of the solar system [MC06]. In all these isotopic ratio techniques, from paleoclimatology to planetary science, the isotope production requirements are for measurement standards.

Naturally occurring U, Th and Ra isotopes, called the Uranium decay-series (U-series) in geology, exhibit various geochemical properties. The chemical fractionation of these isotopes occurring on various time scales in many geological environments in combination with the vast difference in the physical half-lives of ^{238}U, ^{234}U, ^{230}Th, ^{232}Th and ^{226}Ra have long been used as geochronologic tools for processes such as magmatic differentiation or deposition of carbonate rocks [CO03, ED03]. Modern understanding of their behaviors during low temperature water–rock interaction, U-series isotopes in soils and riverine sediments have been shown to have great potential as a novel chronometer of the rates and duration of chemical weathering at Earth's

surface [GR10, MA10]. The determination of U and Th concentrations and $^{234}U/^{238}U$ activity ratios were performed by mass spectrometry, using very high purity ^{233}U and ^{229}Th (very low contamination from both ^{230}Th and ^{232}Th) as the internal standards for the calibration of the mass spectrometer [MA12]. The Calutron-enriched ^{233}U, batch UTHX001 (known as the Y-12 cow), is the only source in the U.S. and Europe that could yield ^{229}Th with required purity for this application.

Solid-state physics

In solid-state physics, vibrational spectroscopy methods, such as Brillouin light scattering or Raman spectroscopy, play a major role in using "isotope labeling," in applications such as identifying the origins of meteorites, or magnitude of atomic displacements in a complex molecule. In superconductivity, the shift in transition temperatures with isotopic substitution is a well-established approach to understand the mechanisms of formation of Cooper pairs and their physical location inside complex crystals. The presence of mixed isotopes also acts as scattering centers in an otherwise perfect crystal, reducing cooperative behavior of atoms with substantially reduced thermal conductivity. Nuclei with unpaired spins can couple with electron spins, and the longer relaxation time of the nuclear spin offers potential as a solid-state quantum memory. Isotopically enriched silicon or germanium-based semiconductors lend themselves for engineered nanostructures with phase coherence quality suitable for solid-state quantum memory devices.

One of the long-standing goals has been to develop a mass standard based on fundamental units. Achieving this goal is an ongoing struggle, but isotopically pure ^{28}Si offers a possibility. The current approach, dubbed Avogadro's project, is an ongoing international collaboration between laboratories in Germany, Italy, Belgium, Japan, Australia, and U.S.A to redefine the kilogram in terms of the Avogadro constant. The Avogadro constant is obtained from the ratio of the molar mass to the mass of an atom, and it is known to an uncertainty of 0.1 ppm. The goal is to reduce this to 0.01 ppm by measuring the volume and mass of isotopically pure silicon spheres. For a crystalline structure such as silicon, the atomic volume is obtained from the lattice parameter and the number of atoms per unit cell. The atomic mass is then the product of the volume and density. The limiting factors are the variability from sample to sample of the isotopic abundances of Si and the content of impurities and vacancies. Thus, kilograms of isotopically pure ^{28}Si are needed.

Chemistry

In chemistry, elusive transition states in reaction chemistry can be revealed through isotopic labeling. Exploiting the variations in nuclear energy levels between different isotopes leads to isotope-based spectroscopic methods, such as *Mössbauer spectroscopy*, which is a major research tool across many scientific disciplines.

Modern theories have encouraged attempts to forecast both electronic and chemical properties of superheavy elements. In this regard, relativistic effects come into play and the chemical and physical properties may not extrapolate from the lighter elements, raising questions about the reliability of classical empirical estimates of thermodynamic properties extended to the heavy elements. Only limited thermodynamic data are available for actinide elements, so investigations of the chemical and physical behavior of actinides is timely.

Mössbauer spectroscopy: Decay of ^{57}Co, through an electron capture process to ^{57}Fe, provides an ideal parent/daughter relationship that lends itself through Mössbauer spectroscopy to study hyperfine interactions in magnetism, lattice dynamics, and local atomic structure in condensed matter with an unprecedented energy resolution of 10^{-13} or better. The Mössbauer effect is related to recoilless absorption and emission of gamma-rays from nuclei bound in a solid. Today many of the parent/daughter isotopes are purchased from Russia, which is a cause for concern for the scientific community. More than half of the elements in the periodic table have Mössbauer active nuclei. In order to conduct the experiments, however, there is also a need for a suitable parent isotope. For example, the most common Mossbauer probe of all times, ^{57}Fe, needs a parent, ^{57}Co, to decay via electron capture to populate the 5/2 isomeric state of ^{57}Fe, which, in turn, cascades down to the 3/2 spin state at 14.4 keV above ground state, and finally, to the ground state.

Since the discovery of this effect in 1957, which resulted in the award of the 1961 Nobel Prize to its discoverer, Rudolph Mössbauer, over 55,000 scientific refereed papers have been reported and a total of 114 isotopes have been used. Since 1985, it has become possible to use synchrotron radiation as a radiation source instead of a radioactive isotope, and since 1995, it has become possible to record the phonon density of states of materials containing one or more Mössbauer isotopes. In a recent study the partial phonon density of states of all elements in a technologically important material, a skutterudite compound of $EuFe_4Sb_{12}$, has been measured. This material has the much sought-after "phonon glass-electron crystal" quality that increases the figure of merit in thermal-to-electric heat conversion efficiency for the radioisotope thermoelectric generators (RTGs). ^{151}Eu, ^{57}Fe, and ^{121}Sb all are Mössbauer active. As a result of this nuclear resonant inelastic x-ray scattering study using all three isotopic resonances of Eu, Sb, and Fe, it has been demonstrated that Eu atoms in the cage have an uncoupled-mode "rattling" vibrational mode at 7 milli eV. The Mössbauer isotopes that are exploited in such studies include ^{57}Fe, ^{83}Kr, ^{119m}Sn, ^{121}Sb, ^{125m}Te, ^{149}Sm, ^{151}Eu, ^{161}Dy and many more.

Chemistry of Heavy Elements -- Chemistry of Francium: The short half-lives of all of its isotopes ($t_{1/2} \leq 22$ min) have made francium one of the least studied among the naturally occurring elements. From the theoretical point of view, francium is a gateway to understanding heavy elements, a gateway recently thrust open by advances in computational methods, isotope-production techniques, and spectroscopy via atomic laser trapping. Relativistic effects are already important in francium and open a fascinating area of study. Indeed, properties such as electron affinities and van der Waals coefficients do not extrapolate from the lighter alkali metals to francium, raising questions concerning the reliability of classical empirical estimates of thermodynamic properties extended to the heavy elements. In fact, little thermodynamic data exist for francium.

In exploring the chemistry of the heaviest elements experiments [HA03] have demonstrated an enhanced Fr-affinity for certain molecules [DE13] (see Figure 4) that have a known affinity for Cs [UN94,MO05]. The short-lived isotope ^{221}Fr ($t_{1/2}$ = 4.8 min) was used in these experiments, and because of its short half-life, it could study equilibrium effects. In ongoing experiments, the standard Gibbs energy of partitioning of Fr^+ ion between water and nitrobenzene has been determined to be 14.5 ± 0.6 kJ/mol at 25 °C, the first ever Gibbs energy of partitioning for francium in particular and the first ever solution thermodynamic quantity for francium in general.

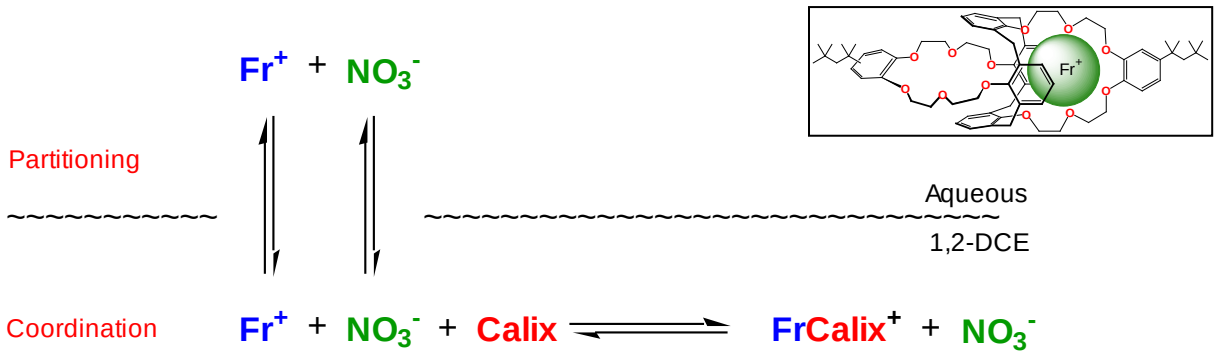

Figure 4: Fr^+ partitioning between aqueous and organic phases, and structure of calix [DE13] arene-bis(benzocrown-6) (upper right)

This value enabled the ionic radius and standard Gibbs energy of hydration for Fr^+ to be estimated, the radius being significantly smaller than previously thought [DE13].

Chemistry of Heavy Elements – the Actinides: The actinides are the heaviest elements for which detailed characterization of physical and chemical properties is feasible. The heaviest element for which macroscopic physical properties have been reported is fermium, element 100, using two nanograms of ^{255}Fm ($t_{1/2}$= 20 h, α). As the actinides are the experimentally accessible elements with the greatest number of protons and electrons, they present new chemistry not seen elsewhere in the periodic table, including effects due to relativity because the electrons in proximity to the highly-charged nucleus exhibit velocities approaching the speed of light. Other effects unique to the actinides are due to bonding participation of electrons in the 5f orbitals; in lighter elements the s, p and d orbitals are chemically active—the occupation of 5f orbitals introduces new and unpredictable physical and chemical effects. In addition to fundamental interest in the far reaches of the periodic table, several of the actinides are of substantial importance due to technological applications, particularly in the realm of new advanced energy sources. The study of actinide science requires the availability of radioactive isotopes, with a particular need for rare isotopes with low specific activities that allow experiments to be performed safely.

Efficient separation of the trivalent actinides, Am and Cm, in the nuclear fuel cycle remains an ongoing scientific challenge, the study of which is revealing new aspects of the chemistry of these neighboring elements. Most Am/Cm separation approaches employ differences in chemical binding to separation ligands, which are generally small due to the very similar chemistries of Am(III) and Cm(III). As an example of the progress possible with further research, a recent study employed crown ether based ligands for the separation of Am(III) from Cm(III) with an unprecedented selectivity [JE14]. The particularly novel aspect of this result was the reversal of the typical order of complex stability, which was explored by theoretical calculations and attributed to steric constraints in the crown ether ring for larger 5f-element cations.

Recent years have witnessed several important advances in actinide physics and chemistry by utilizing specially produced isotopes, notably ^{242}Pu, ^{244}Pu, ^{243}Am, ^{248}Cm and ^{249}Cf [HE13, PO14, LA12]. A primary focus of actinide chemistry continues to be on plutonium, one of the most

chemically diverse and fascinating elements in the periodic table, and perhaps also the most important element in nuclear technology. Plutonium exhibits a plethora of oxidation states, from III to VII (and perhaps VIII), and furthermore has a sufficient number of 5f electrons to introduce substantial complexity in bonding and reactivity. Plutonium studies in recent years have ranged from solid state to solution to gas phase, and in virtually all realms of physical science. Of particular significance in recent years has been the synthesis and characterization of plutonium oxide nanoclusters. Plutonium is notorious for agglomerating in solution, resulting in suspended colloids and precipitates. Such deviations from typical actinide solution speciation result in unanticipated behavior of plutonium in the environment and technological processes such that understanding the nature of these species, and ultimately controlling their chemistry, is critical.

Evidence for Changing Electronic Behavior Late in the Actinide Series: The actinides elements are thought to be dominated by the trivalent oxidation state in all elements beyond plutonium. In fact, plutonium represents a tipping point in the series where 5*f* electrons start to localize and accessing them with oxidants becomes quite challenging. Beyond plutonium, oxidation states beyond 3+ are transient unless strong complexants are used to impart stability. Concomitant with the loss of redox activity is further localization of 5*f* electrons to the point that americium metal is a superconductor at low temperatures. What is seldom recognized is that further in the actinide series a second transition starts to take place where the 2+ oxidation state becomes thermodynamically stable. Californium is the first element where the divalent state becomes accessible at reasonable electrochemical potentials. It is shown that californium represents a second tipping point in the series, and that this transition corresponds to the strongest evidence for covalent bonding with a variety of ligands [PO14]. Large ligand-field effects are observed that are stronger than anywhere else in the actinide series with 3+ ions. Recent hypotheses suggests that these effects will be enhanced later in the series. In order for this work to be carried out there will need to be renewed production of berkelium, einsteinium, and fermium.

Engineering

Radioisotope thermoelectric generators: A very practical and important power-source type application (in cases where a few hundred watts of power is needed for a long time) is the radioisotope thermoelectric generator *(RTG*), a device that uses an array of thermocouples to convert the heat released by the decay of a suitable radioactive material into electricity. They have been used successfully as power sources on 23 spacecraft since 1961, including planetary (Pioneer, Voyager, Galileo, Ulysses, Cassini, New Horizons), Earth orbit (Transit, Nimbus, LES), lunar surface (Apollo ALSEP), and Mars surface (Viking) probes. RTG also have been used in very practical and large-scale applications like powering pacemakers and other implanted medical devices, where microwatts of power are needed. Other remote applications include; weather and tsunami warning stations, navigation signal stations, radio beacons, undersea deep-water installations, and transmitters at remote locations with hostile environmental conditions.

Various technologies are under development including Stirling heat engines (devices that convert heat energy into mechanical power by alternately compressing and expanding a fixed quantity of air or other gas, the working fluid, at different temperatures) and thermo-photovoltaic devices using piezoelectric materials combined with MEMS (micro-electro-mechanical systems) technology.

Radioisotopes like ^{90}Sr, ^{210}Po, ^{238}Pu, and ^{244}Cm have been used in RTG, and the power output can be as high as 2.5 W/g and 26 W/cc for ^{244}Cm. The most common isotope for RTG applications is ^{238}Pu, an alpha emitter; thus it has the lowest shielding requirements and long half-life (87.7 years) high density (19.6 g/cc) and reasonably high energy density (0.56 W/g). While there are concerns for environmental and other safety concerns, potential improvements in energy efficiency and prevention of radiation damage for some piezoelectric converters may increase the electrical conversion efficiency by a factor 10 or more, thus making RTGs even more attractive power sources and, in some cases, perhaps the only alternative. Therefore, the need for alpha emitting isotopes of such as ^{210}Po, ^{238}Pu, ^{244}Cm, and ^{241}Am, and beta-decaying ^{90}Sr will continue in the future [KO06].

While ^{90}Sr is a low cost isotope for this application, ^{244}Cm could be more suitable in some applications because of its high power (however, the costs associated with providing this isotope may be a barrier to its use). It can be recovered through proven methods in large quantities in spent nuclear reactor fuel. Several issues remain for ^{106}Ru, ^{144}Ce, ^{210}Po, or ^{242}Cm, such as difficulties associated with the fabrication of ^{210}Po source and higher shielding requirements for ^{106}Ru, ^{144}Ce. Continued discoveries in thermoelectric materials like transition metal antimonides, skutterudites, PbTe, and SiGe, combined with computer aided design of layered systems, provide a promising prospect for RTGs.

Applications of lithium isotopes: The stable lithium isotopes, ^{6}Li, and ^{7}Li, have long been used in a number of extremely important research and engineering applications due to their special nuclear and chemical properties and low density. ^{6}Li is particularly important for thermonuclear applications such as nuclear weapons, targets for tritium production and fusion reactors but is also used in advanced battery research. ^{7}Li is currently used primarily for research and for pH balance in boiling and pressurized water nuclear reactors. Typical isotope sales over the past five years have been about 20 kg of ^{6}Li and 4 kg of ^{7}Li per year. The primary technique previously used for lithium isotopic separation was a mercury amalgam process, with significant environmental and human health concerns (this process is now banned). As a result, all current U.S. production of ^{6}Li is obtained from reprocessing material in the dismantlement of nuclear weapons. There are several future applications that would result in a major increase in lithium utilization, far beyond current quantities. Advanced fusion power systems could require 10000-40000 kg of ^{6}Li per application. NASA is also considering ^{6}Li as the light-weight shielding of choice for future space based reactors. Typically 1000 kg of ^{6}Li would be needed per reactor. Lithium is also used as the working fluid in a number of advanced nuclear reactor concepts, such as the Advanced High Temperature reactor. In these cases, separated ^{7}Li is required to minimize tritium production. The requirement for a 1 GWe commercial reactor is estimated to be about 25000 kg of 99.995% enriched ^{7}Li. New processes need to be developed and proven to address such large-quantity and high-enrichment needs in an environmentally responsible fashion.

This section has highlighted a few of the many uses of stable and radioactive isotopes in the physical sciences and engineering. Another example with perhaps the highest economic impact is the use of isotopes in well logging to allow proper operation of oil and gas wells and provide an accurate inventory of reserves (see Sidebar 5). All of the applications discussed in this section critically rely on the availability of these isotopes. The priorities and new opportunities that would be opened by increased availability are discussed in section 4.B.

3.C: National Security and Other Applications

The uses of isotopes in national and homeland security applications range from large-scale use in radiation detectors worldwide to use in research associated with the certification of the nuclear stockpile. They have become an indispensable part of the means we use to characterize nuclear processes, and are the heart of probes used to interrogate suspect materials. From the use of deuterium and tritium in neutron generators to the calibration of methods used in nuclear forensics, many missions use radioactive and stable isotopes of the lightest to the heaviest elements. In order to inform a discussion of the key future needs for isotopes, it is instructive to first review the scope of research and applications in this area.

Over the course of this study, the subcommittee heard presentations from several agencies outlining the activities they conduct, and the attendant need for isotopes, including the Domestic Nuclear Detection Office (part of the Department of Homeland Security), the National Nuclear Security Administration (NNSA - a semiautonomous organization within the Department of Energy), and the Department of Defense. These entities provide input to the Isotope Production Program through the Federal Isotope Workshop, and in some cases the Isotope Program participates in other working groups defining needs. These interactions are useful in the coordination of production needs and activities. Additional input was provided by the DOE national laboratories, which serve as both production sites and in some cases customers for the isotopes used in research and development.

It is worth noting that other parts of the Department of Energy have a role in ensuring the supply of certain isotopes. NNSA provides (or has provided in the past) excess materials that serve as feedstocks for the availability of isotopes for distribution (such as ^{3}He separated from tritium stores, ^{241}Am generated from decay of weapons grade plutonium, or separated inventories of ^{6}Li and ^{7}Li). The Office of Nuclear Material Integration (ONMI) coordinates DOE-wide use, procurement, disposition, and storage of accountable nuclear materials. This includes both fissile materials and source materials used to produce fissile materials, along with select other isotopes of special interest. Through an annual planning cycle, this Office identifies demands within DOE for these materials. The Heavy Isotopes Lead Material Management Office (HILMMO) works directly with NIDC; the Isotope Program is also a member of the DOE Nuclear Materials Advisory Board, which is led by ONMI.

Uses of isotopes in national security research and applications can be broadly divided into four categories: radiation detection (for safeguarding known nuclear facilities, verifying compliance with treaties, and the identification and interdiction of illicit facilities and materials); analytical and radioanalytical chemistry (for destructive analysis for safeguards and forensics applications); research in weapons physics; and power sources and neutron generators.

Radiation Detection

A number of different missions (and different agencies) rely on radiation detection instrumentation. These applications may require particular isotopes in the manufacture of instrumentation, or alternatively programs may use radioactive materials as calibration sources or in radiation-generating devices for active interrogation. While common basic measurement methods (detection of neutrons, gamma rays) are used in all of these missions, some applications require more sensitive methods to determine mass of fissile material.

Sidebar 5: Isotopes – The Critical Element to Cost Effective Oil & Gas Exploration

Isotopes are a key element to support the exploration, and subsequent efficient and cost effective production of oil & gas. There are over 360,000 oil and 460,000 gas wells in the US today that were evaluated, are maintained and are optimized for production using isotope techniques. This work covers more than three-quarters of all US wells.

After evaluating potential oil and gas drilling sites by seismic or other methods, a well bore is drilled to enable petroleum engineers and geologists to evaluate the physical structure and chemical properties near the well bore by electrical, magnetic, acoustical, physical, and most critically, nuclear surveys using radioisotopes through the process of well logging.

Well logging was first used in 1927 by Schlumberger lowering an electrical sonde, suspended on a cable, at differing depths in a borehole, to create a graph of the electrical resistance of the earth, to deliver a data log of resistivity, which indicated the location of oil in the formations. Over the years, other methods/instrumentation of well logging were developed that further refined the evaluation of the potential of the reservoirs to produce oil and gas economically.

Isotopes play a critical role in the well logging arsenal of analysis techniques. Rock porosity is determined primarily by using density, neutron and some acoustical logging methods. Formation density is established using gamma rays from a ^{137}Cs source (~2 Ci) – the absorption of gamma rays is a measure of the density of the formation and therefore indicates the type of formation materials like limestone, sandstone and dolomite. From that data, the porosity of the formation can be determined. By using neutrons (from ^{252}Cf or ^{241}Am/Be sources of ~15 Ci), which are attenuated by the hydrogen in oil and water, a measurement of the neutron absorption also indicates and further refines the porosity measurement of the formation. By combining these porosity measurements with resistivity and other measurements, an evaluation of the formation can be made to take the next steps of setting pipe (casing) and producing the well economically.

Radioactive markers (^{241}Am) are used in casing joints for depth control. ^{3}H neutron accelerators evaluate reservoir depletion levels behind the casing. ^{137}Cs interface logs verify fluid levels in storage caverns. Tracers using ^{131}I can indicate fluid movement within and on the other side of the casing. Radioactive tagging is used for hydraulic fracture analysis (^{131}I, ^{192}Ir, ^{46}Sc, ^{124}Sb) using activities from 1 μCi to 10 mCi. Energy compensation sources, either ^{241}Am, ^{137}Cs, or ^{226}Ra, with activity typically between 1 to 500 μCi, are used in calibration.

The well log acts both as a key identifier initially in exploration phase for the location of oil & gas, but then subsequently in the quality and effective management of production in new and operational wells. This supports estimates of what the well can produce, how efficiently and effectively the hydrocarbons can be produced, and what the total capacity and reserves are of the well. This information drives the value of the asset, and all that is associated for the companies drilling and producing the oil fields, from the ability to borrow and invest, to being able to accurately forecast increasing stakeholder value.

Among the most noteworthy applications of radioisotopes in the manufacture of radiation-detection devices is the use of ^{3}He for neutron detection in the production of radiation portal monitors, used to detect radioactive materials in transit. Concerns regarding the availability of ^{3}He were identified in the 2009 NSACI report [NSACI09]; shortages with the supply of this isotope have been largely mitigated since then (see Sidebar 6). Alternative isotopes have been

identified that can serve as conversion material in these detectors, including ^{10}B-lined proportional detectors, ^{10}B enriched boron trifluoride proportional detectors, and ^{6}Li scintillators. Additional research is being conducted on the use of these and other isotopes (e.g. ^{35}Cl) in detector materials.

Efforts to manage the proliferation of weapons-usable materials concentrate on applying safeguards at declared nuclear material processing facilities and on inspections to verify compliance with treaties. Nuclear safeguards are measures to verify that countries comply with their international obligations not to divert nuclear material from civilian power programs for weapons programs. Under safeguards agreements, the host state provides the International Atomic Energy Agency (IAEA) with declarations of its nuclear materials (how much and where), along with information about the associated nuclear facilities. Verification of these declarations is provided in part by inspections, including direct measurements of materials.

Methods for non-destructive evaluation of mass (and enrichment levels, in the case of uranium) include gamma ray spectroscopy, neutron coincidence measurements, and calorimetry employing radioisotopes for both calibration and as sources for active interrogation of systems. [RE91, ASTM00]. Calibration of detectors utilizes gamma-ray sources (e.g. ^{152}Eu, etc.).

Measurements are intended to determine both the type and quantity of the nuclear material. Although the high density of plutonium and uranium results in significant self-attenuation in gamma spectroscopy, this technique can used for the assay of waste or scrap through the use of transmission-corrected assay methods. In this method, a high resolution gamma-ray spectrometer is used to characterize the fissile material through identification of characteristic energies of gamma rays. In order to correct for self-attenuation, an additional scan of the container is performed with a transmission source to determine attenuation by the materials in a container as a function of gamma-ray energy. The transmission source is a radioisotope with a reasonably long half-life (>100 days) chosen to have gamma-ray emission lines that closely match those of the isotope of interest (e.g. ^{75}Se may be used as a transmission source for ^{239}Pu, and ^{169}Yb for ^{235}U).

Neutron counting is a technique used to measure neutrons emitted by fissioning isotopes. It is normally used to quantify uranium and plutonium. Active techniques involve interrogation of the sample with neutrons from a neutron source or a neutron generator. The neutrons emitted from this induced fission are measured by the detector and counting system. These instruments take advantage of the unique characteristics of the neutron spectrum of ^{252}Cf sources for their efficiency calibration.

^{252}Cf can also be used as a neutron source for irradiation to induce fission in a sample. For example, the mass of uranium can be determined by counting delayed neutrons from the fission produced by irradiation from a neutron source.

Analytical and Radioanalytical Methods

Destructive methods are also commonly employed to characterize materials in national security missions. Analytical chemistry is required to support the manufacturing and surveillance of nuclear weapons pits for the U.S. stockpile. Analytical methods are used in the evaluation of

Sidebar 6: Ensuring the Supply of ^{3}He Has Been Important to the National Security Community

Radiation portal monitors (Figure 5) are an integral component of the Nation's overall system for screening individuals, vehicles, and cargo for detecting illicit transport of radiological or nuclear materials. One common technology used in portal monitors for neutron detection involves an isotope of helium, helium-3 (^{3}He). Radiation portal monitors have been deployed domestically and overseas by the Departments of Homeland Security, Energy, and Defense. ^{3}He detectors became favored, due to a combination of characteristics, including high neutron detection efficiency, ability to discriminate between gamma radiation and neutrons, and relatively low cost. The Isotope Program supports the extraction of ^{3}He from tritium stockpiles managed by the National Nuclear Security Administration and made available through the Department of Energy [GA11A].

Figure 5: Portal monitor containing ^{3}He in use scanning a cargo containing truck

In 2008, the U.S. Government identified a shortage in the availability of ^{3}He, driven by an increase in demand and reduced availability [GA11B]. In the 2009 NSACI report, the subcommittee recommended that a focused study be undertaken, assessing R&D necessary to address this shortfall [NSACI09]. The subcommittee further noted that NNSA and DHS should evaluate alternative technologies for neutron detection.

In response to the need, the Office of Nuclear Physics played a lead role in an interagency working group reporting to the White House National Security Staff, working with multiple agencies to address both means of increasing the supply and managing the demand of this strategic isotope. Approaches evaluated for increasing supply included seeking alternative sources, encouraging recycling and reuse, and investigating novel production and separation methods. In addition, the government prioritized use of the existing stockpiles of ^{3}He, and aggressively sought to develop and deploy alternative technologies for neutron detection.

As a result of these activities, the shortfall was mitigated, and the current supply of ^{3}He is projected to meet Federal agency needs well beyond 2040. The Department of Energy has successfully addressed the availability of this important isotope.

environmental samples collected in monitoring of declared nuclear facilities as part of safeguards implementation. Similar methods also serve as part of the suite of forensic tools employed in the examination of materials outside of regulatory control. Radiochemical analysis founded on our history of weapons tests serves as the basis for measurements that could be made on an unknown nuclear explosion. A common characteristic among all of these applications is the need for precise measurements. Isotopes serve an important role in the development of these methods, as well as in ensuring the calibration and validation of instruments used to perform the measurements. For the majority of methods discussed here, research quantities of isotopes with high isotopic purity are required.

As part of a robust quality program for analytical characterization, it is necessary to calibrate measurements using reference materials of known composition. Since the overall matrix of the

sample to be analyzed can have an effect on the analytical measurement, care is often take to ensure that the substrate of the reference material is similar to that of the unknown sample ("matrix matched"). The production of certified reference materials (CRMs) containing radioisotopes of interest is therefore important to analytical methods in these programs [LE09].

Multiple measurements are used in the analysis of samples. These include elemental analysis of major constituents and analysis of metal and non-metal minor constituents or impurities in the sample. It may also be necessary to analyze the distribution of isotopes for any given element. A specialized method employed in the analysis of radioactive materials is radiochronometry, a method designed to determine the age of a material. A radioactive material (the "parent") decays to other elements/isotopes ("daughters") at known decay rates. By measuring the ratio of parent-daughter pairs, it is possible to calculate the time that has elapsed since the sample was chemically separated. Dating a material by this method is useful both for the identification of an unknown sample, and to confirm declarations regarding the age of production of a material. Many methods may be employed in the laboratory in combinations to provide the necessary characterization data on any given material (Table 3). Overall physical characteristics may also be examined, such as the crystalline structure of the sample or the morphology of a solid sample by x-ray diffraction or microscopy methods.

Table 3: Analytical methods used in the characterization of radiological and nuclear materials

Analytical Method	**Information**
High Resolution Gamma Spectrometry (Radiochemistry); Gamma Scanning	Isotopic composition of Np, Am, U, and Pu, fission products; Identifying SNM distribution
Alpha/Beta Spectrometry (Radiochemistry)	Isotopic composition of Np, Am, U, and Pu, fission products, dose measurement
Titration	U and Pu content
Coulometry	Pu content
Mass Spectrometry	Isotopic composition of U and Pu, impurities, age, stable isotope ratios, U and Pu content
Thermal Ionization Mass Spectrometry (TIMS), Isotope Dilution Mass Spectrometry (IDMS), Inductively Coupled Plasma Mass Spectrometry (ICP-MS)	
Micro X-ray Fluorescence	Elemental Distribution
Plasma Methods	Impurities, trace elements, elemental distribution
(ICP-AES, ICP-MS)	
Atomic Absorption	Mercury
Interstitial Gas Analysis	Impurities (C, H, N, O, S, & halogens)
Optical/Electron Microscopy	Particle size, elemental distribution, grain size, porosity, surface roughness.
Particle Size Analysis/Pycnometry	Particle size/density
X-ray Diffraction/Differential Scanning Calorimetry	Composition/phase
Neutron Activation Analysis	Isotopic and elemental analysis

The availability of isotopes is necessary to meet the demand for certified reference materials and calibration standards. The most common standards employed are those required to support calibration of instruments for direct measurement of analytes. An example would be a certified reference material containing known quantities of an isotope (by mass or by activity) for verification of instruments and methods. Other isotopes are used as spikes or tracers in analytical measurements.

Weapons Physics Research

NNSA is responsible for maintaining a safe, secure, and reliable nuclear weapons stockpile. With the cessation of nuclear testing in 1992, it has become necessary to develop sophisticated simulations of weapons performance that incorporate knowledge of the physical phenomena and materials behavior that occur within a nuclear explosion. Among the physical phenomena that must be incorporated into these models are the many different simultaneous nuclear reactions that take place in the high neutron fluence environment present during an explosion. Nuclear data serves an important role; new data supports an understanding of the stockpile by reducing uncertainties incorporated into models and codes used to describe such important phenomena as energy production through fission and fusion reactions.

These simulations must be validated by comparing measurements associated with historic U.S. weapons tests against predicted values. This generates another need for nuclear data. In these tests, radiochemistry served as one of the main diagnostics of weapons performance. Radiochemical analysis of debris provided information on device performance. Weapons radiochemistry as an interpretive tool also relies on accurate nuclear data to interpret the complicated elemental and isotopic signatures that arise in debris. Historically, specific isotopes were also employed as "detectors" to diagnose the energy output of the event; capture (n,γ) , (n,2n), (n,p), (n,f) and charged particle reactions associated with these radchem detectors serve to further connect the wealth of data from the history of underground tests with the certification of modern weapons codes.

Experimental nuclear science has long had a role within the nuclear weapons science program. Isotopes serve an important purpose in these studies as target materials for the study of neutron-induced reactions. Target materials can include actinides (for the study of fission reactions) or actinides/fission products/detector materials (for the study of neutron capture reactions). High isotopic purity materials are required as targets for this research. This highlights the continuing need for stable isotope enrichment and a radioactive isotope separator. While relatively fewer experiments have been conducted using short-lived targets, opportunities exist for these experiments at facilities such as FRIB in the future. There are many opportunities for research with longer-lived isotopes utilizing harvesting techniques being developed at a number of laboratories.

It should be noted that these efforts to improve weapons modeling capabilities have benefits for related missions in post-detonation nuclear forensics.

Other Security Applications

Select other applications rely on the availability of isotopes. One example is the use of ^{63}Ni in detectors utilized by the Transportation Security Administration (TSA) in screening for explosives residue. These detectors are based on ion mobility spectrometry, an analytical technique used to separate and identify organic molecules at the trace level through their ionization and separation by mobility in a carrier buffer gas. In commercial implementation the beta-emitting ^{63}Ni serves as the ionization source.

The radioactive nickel isotope is prepared by neutron irradiation of isotopically enriched targets of stable ^{62}Ni. The Isotope Program serves as the exclusive source for North America for both the ^{62}Ni used in targets as well as for the ^{63}Ni product.

Chapter 4: Research Opportunities Using Isotopes

Chapter 3 above reviewed the uses of isotopes and identified many examples of their unique contributions to our lives. In this chapter we review research opportunities that have the promise of further extending the impact of isotopes on the same three broad categories of application: Biology, Medicine and Pharmaceuticals; Physical Sciences and Engineering; and National Security and Applications. The areas identified should broadly define the priority focus of IDPRA's activities for the period covered by this Long Range Plan.

4.A. Research Opportunities with Isotopes in Biology, Medicine and Pharmaceuticals

While isotopes are used routinely in medical practice, the development of new isotopes is essential to the progression of this important field. New isotopes are crucial to the development of new molecular imaging agents and targeted radiotherapeutics. Additionally, the development of theranostics, or matched imaging and therapeutic isotopes is expected to have great impact on the advancement of personalized medicine (see Sidebar 7).

Future Isotopes for Imaging

PET Isotopes As mentioned in Chapter 3, due to its high sensitivity and resolution, PET is growing rapidly as an imaging technology. However, the efficacy of this method is based on instrumentation, as well as the creation of innovative and reliable probes. Research in the area has been typically focused on 4 main radioisotopes (^{11}C, ^{13}N, ^{15}O and ^{18}F). However, these are not without limitations; their short half-lives restrict radiopharmaceutical development to those that examine fast biological processes. Research into new PET isotopes has gathered a lot of momentum in recent years in a bid to overcome these limitations.

New isotopes can allow for the innovative design and integration of a broader range of PET tracers to investigate biological activity and processes. Several targeting pharmaceutical agents slowly congregate at the site of a tumor, meaning longer-lived isotopes are often required to optimize the accumulation in target tissue, as well as abate the non-target uptake. Recent studies have focused on the PET radiometals: ^{68}Ga, ^{64}Cu, ^{86}Y and ^{89}Zr, some of which can be used with their theranostic isotope pair in therapy regimens. The employment of these non-traditional radioisotopes is restricted by their availability.

Recent years have seen PET make the transition from a new technology to the preferred method for non-invasive imaging. Its sensitivity in the nano- to pico-molar range allows analysis and probing of biological processes at a cellular or molecular level, without hindering normal physiological functions. As well as target occupancy and disease staging, non-invasive PET imaging produces a map for drug delivery and distribution within the human body. Thus, it is invaluable for understanding pharmacokinetics (what the body does to a drug) and pharmacodynamics (what the drug does to a body).

A success story in this area is [^{68}Ga]DOTATOC. This is a peptide-based imaging agent that specifically targets a receptor (somatostatin) overexpressed in neuroendocrine tumors. As can be seen in Figure 6, this agent can enable visualization of very small tumors that may not be observed on conventional CT or MRI scans. This is also an important theranostic agent as the

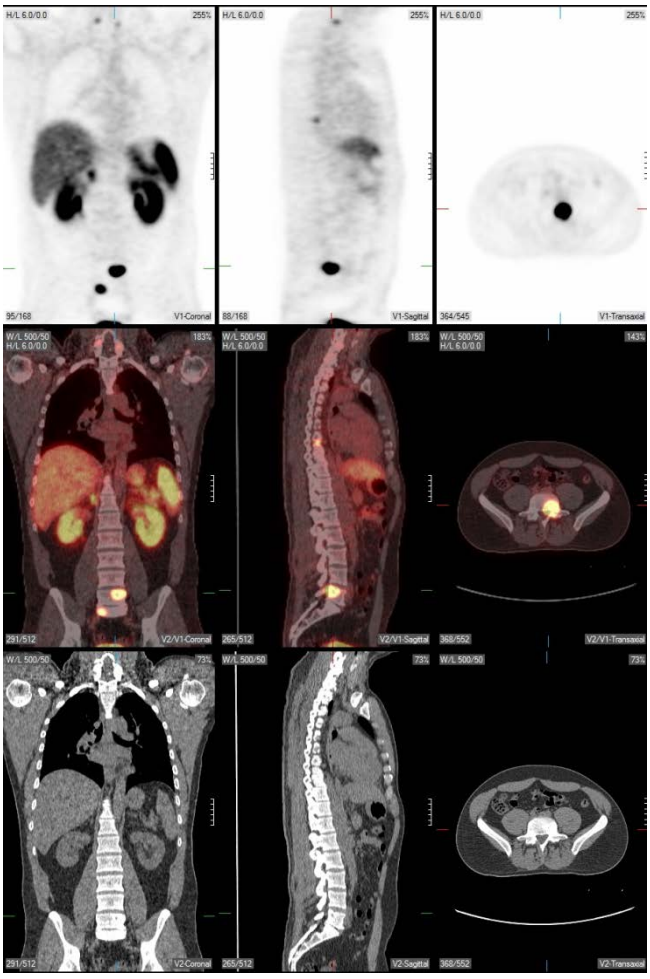

Figure 6: ^{68}Ga DOTATOC scan in a 41 year old man with "atypical carcinoid" in the right upper lobe of the lung removed surgically in February, 2013. Top: ^{68}Ga DOTATOC PET scan illustrating radiopharmaceutical uptake in several metastatic tumor sites. Center: Co-registered PET/CT scan to allow for anatomical localization of tumor sites identified by ^{68}Ga DOTATOC PET Bottom: Anatomic CT scan. *Image courtesy of Dr. Michael Graham, University of Iowa.*

companion therapeutic has been shown to have dramatic effects when used in patients that have a positive [^{68}Ga]DOTATOC scan [KR14].

Ideally, a PET isotope should have both a low positron energy and a high positron decay branching ratio. Further, it should have a physical half-life that matches the biological half-life of the molecule or biological process being probed and should be long enough to allow for radiochemical synthesis within two half-lives of the isotope's decay.

While ^{89}Zr is now commercially available, other longer-lived useful positron emitters (some of which have theranostic applications) include ^{52}Mn, ^{44}Sc, ^{45}Ti, ^{86}Y, ^{76}Br, ^{48}V and ^{55}Co. The availability of a toolbox of these isotopes is important as changes in chemistry and half-life are necessary to create specifically targeted probes with good imaging properties.

Isotopes for Theranostics: With the advent of personalized medicine, where the treatment of the disease is tailored to a specific patient, there is a need for production of *theranostic radioisotopes* (see Sidebar 7). Theranostic radioisotopes, theranostic radioisotope pairs and matched radioisotope pairs can provide valuable diagnostic information on the radiopharmaceutical to be administered for therapy before the therapeutic dose is given. This technique, where the use of an imaging agent is employed prior to administration of the radiotherapeutic can help with stratification of patients likely to respond to certain therapies and dosimetry planning on an individualized basis. Most importantly, treatment will not be undertaken unless the diagnostic indicators provide evidence that it will (or may) be successful. This personalized medicine approach not only helps keep physicians from administering a radiopharmaceutical that has little or no chance to help the patient, but also permits a more rapid treatment change to another approach that will be effective in that patient. The table in Sidebar 7 lists theranostic isotopes and their half-lives.

As mentioned in Chapter 3, radioisotopes that have particle emissions can be used in therapy of human diseases if they naturally localize to the diseased cells or when they are attached to the appropriate disease-targeting agents. The differences in the three types of particle emissions, beta particles, alpha particles and Auger electrons are described in Chapter 3. Radiopharmaceuticals containing beta-emitting radioisotopes have been investigated the most, as many beta-emitting radioisotopes have been available. Of beta-emitters, the radioisotope that has been most widely used is radioiodine (^{131}I). In addition to Na[^{131}I]I used for thyroid cancer, there have also been two other cancer-targeting radiopharmaceuticals approved by the FDA that contain beta-emitting radioisotopes. Those are Bexxar®, which contains ^{131}I, and Zevalin®, which contains the beta-emitter ^{90}Y. Although fewer studies have been conducted with alpha-emitting radioisotopes, the number of investigations is increasing since their availability is increasing.

As discussed in Chapter 3, radioisotopes with Auger electron emissions have been studied but the short path length of those emissions requires development of sophisticated targeting agents. The Auger cascade (of emitted electrons) is particularly attractive for therapy in a very localized area (μm to nm) and thus holds great promise for development of highly selective agents in the future.

Future Isotopes for Therapy

There are several factors that must be addressed in isotope production to meet the needs of the U.S. medical community for development and application of radioisotopes used for therapy. Most importantly, there continues to be a critical need to increase the availability of a number of therapy radioisotopes. In conjunction with availability, there is a need to obtain high purity and high specific activity of the therapy radioisotopes. Additionally, continued effort is needed to support the development of (alternative) radioisotope production methods that will allow the lowest pricing of the radioisotope so that the medical market can more readily bear the cost.

α-Emitting Isotopes: The tremendous potential that alpha-emitting isotopes have for therapy, particularly blood-borne and disseminated cancers, cannot be achieved until larger supplies are available. The DOE Isotope Program is investing in R&D (still in progress) aimed at increasing the supply of ^{225}Ac. That supply is still inadequate to meet the demand for clinical studies

Sidebar 7: Theranostics and the Transition to Personalized Medicine

Theranostics (also called Theragnostics) is a term referring to radioisotopes and radiopharmaceuticals that can be used for both diagnosis and therapy. Dual function radiopharmaceuticals can play an important role in Personalized Medicine as they can be used to determine if the prescribed therapeutic dose will work in a patient prior to administration. The determination is based on the estimated doses delivered to the disease area and normal tissues obtained from the diagnostic procedure. Ideally, theranostic radiopharmaceuticals are coupled with a radioisotope that has both imageable and therapeutic emissions (a theranostic radioisotope). Such radiopharmaceuticals can be used for evaluation of disease targeting and pharmacokinetics with a small diagnostic dose, then, if appropriate, used for therapy by administration of a much larger dose. Alternatively, as shown in Figure 7, two radioisotopes of the same element (a theranostic radioisotope pair) may be used, one of which has emissions useful for diagnostics and the other having therapeutic emissions. In this case, the theranostic radiopharmaceuticals are identical except for the radioisotope used. These radiopharmaceuticals have the same pharmacokinetics and in vivo stability. A second less favorable alternative is to have two radioisotopes of different, but chemically similar, elements (a matched radioisotope pair). In this later case, the same radiopharmaceutical may be separately coupled to the two different radioisotopes but the in vivo stability may be different, which in turn could alter the pharmacokinetics and disease targeting. Examples of the types of theranostic radioisotopes are provided in Table 4, Table 5, and Table 6 later in this sidebar.

To be effective, theranostic radiopharmaceuticals must have high specific activity. That is to say, the ratio of radioisotope to radiopharmaceutical targeting molecule has to be as high as achievable without damaging the biological properties of the pharmaceutical. The number of radioisotope atoms in an effective diagnostic or therapeutic dose can be very small (depending on half-life), and combining those with a measurable quantity of a pharmaceutical can result in ratios of isotope-to-pharmaceutical that can be of the magnitude of one isotope atom per thousand pharmaceutical molecules. Low specific activity can result in diminished localization of the radioisotope, as there are many more pharmaceutical molecules without the isotope that can compete for binding with cell surface antigens or receptors. Depending on the number of antigens or receptors on the cell, low specific activity can result in less radioisotopes binding to the targets, which can result in poor diagnostics and/or ineffective therapy from the radiopharmaceutical.

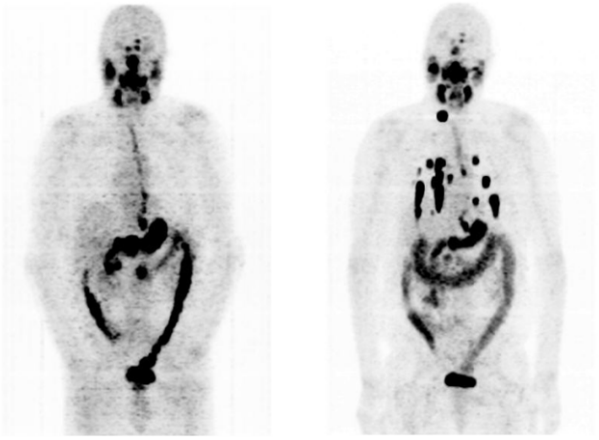

Figure 7: ^{124}I PET images of a patient before and after the administration of the cancer drug selumetinib, which causes increased uptake of radio-iodine into metastatic thyroid cancer. With this theranostic isotope pair, increased uptake of the ^{124}I provides the PET image (the black areas on the image indicate high positron emission from those areas coming from ^{124}I uptake). Since ^{131}I will be taken up in the same areas (and kill cancer cells there) the PET image documents the beneficial effect of selumetinib. The result is a monitored, improved treatment of the tumors [HO13].

Sidebar 7 (cont.) List of Isotopes Usable in Theranostic Radiopharmaceuticals.

Table 4: Theranostic Isotopes (single isotope)

Isotope	Half-life (days)	Imaging Emission(s)* γ or β+ energy in keV (abundance)	Therapy Emission mean energy; keV (abundance)
^{131}I	8.02	364 (82%)	β -; 182
^{186}Re	3.72	137 (9.5%)	β -; 347
^{188}Re	0.71	155 (16%)	β -; 763
^{177}Lu	6.65	208 (10 %)	β -; 134
^{67}Cu	2.58	184 (49%)	β -; 141
^{47}Sc	3.35	159 (68%)	β -; 162
^{198}Au	2.69	411 (96%)	β -; 312
^{199}Au	3.14	158(40%)	β -; 82
^{213}Bi	0.03	440(26%)	β -; 435: α; 8537**
^{117m}Sn	14.0	159 (86%)	Auger; 3.0(93%)
^{195m}Pt	4.0	99(11%); 130(2.9%)	Auger; 7.2(140%)
^{111}In	2.80	171(91%); 245(94%)	Auger; 2.7(100%)

*only emission most likely to be used for imaging is listed; **from ^{213}Po

Table 5: Theranostic Isotope Pairs (same element)

Imaging Isotope (type)	Half-life (hours)	Imaging Emission(s) γ or β + energy in keV (abundance)	Therapy Isotope	Half-life (hours)	Therapy Emission mean energy; keV (abundance)
^{64}Cu (β +)	12.7	278	^{67}Cu (β -)	61.8	141
^{44}Sc (β +)	4.0	632	^{47}Sc (β -)	80.4	162
^{86}Y (β +)	14.7	652	^{90}Y (β -)	64.1	934
^{123}I (γ)	13.2	159 (83%)	^{131}I (β -)	192.5	182
^{124}I(β +)	100.3	687(12%); 974(11%)	^{131}I (β -)	8.02	182
^{152}Tb (β +)	17.5	1337(8%); 1186(6%)	^{161}Tb (β -)	165.4	154
^{72}As (β +)	26.0	1117(64%); 1529(16%)	^{77}As (β -)	38.8	226
^{155}Tb (γ)	127.7	180(8%); 163(4%)	^{149}Tb (α)	4.12	3967 (17%)
^{76}Br (β +)	16.2	1532 (26%)	^{77}Br (Auger)	57.0	1.3 (115%); 9.7 (35%)
^{68}Ga (β +)	1.13	836 (88%)	^{67}Ga(Auger)	78.2	1.0(168%); 7.5(61%)

Table 6: Matched Isotope Pairs (different elements with similar chemistry)

Imaging Isotope	Half-Life (hours)	Imaging Emission(s) * γ or β + energy in keV (abundance)	Therapy Isotope	Half-life (hours)	Therapy Emission mean energy; keV (abundance)
^{99m}Tc (γ)	6.0	141 (89%)	^{188}Re (β -)	17.0	763
^{111}In (γ)	67.2	171(91%); 245(94%)	^{90}Y (β -)	64.1	934
^{123}I (γ)	13.2	159 (83%)	^{211}At (α)	7.2	5870(41%); 7450(59%)*
^{124}I (β +)	100.3	687(12%); 974(11%)	^{211}At (α)	7.2	5870(41%); 7450(59%)*

*7450 keV alpha from Po-211 ($t_{1/2}$ = 0.5 sec)

Note: Theranostic isotopes have diagnostic gamma emissions along with the therapeutic beta emissions. If positron imaging is desired, then theranostic isotope pairs can be used. Astatine-211 has X-ray emissions (e.g. 79 keV; 21%) that may be used for imaging in certain cases, but generally one must use matched pairs with iodine isotopes to obtain patient imaging data. The Tables show major isotopes, but are not inclusive of all isotope possibilities.

currently being conducted, or planned for the future. Similarly, the Isotope Program is investing in R&D to increase the availability of ^{211}At. This is an ongoing effort that, to date, has increased the availability of ^{211}At, but it is still very limited. Efforts to increase the current production of ^{225}Ac and evaluate alternate production routes should continue to be considered a high priority. Making ^{211}At available to researchers and clinicians is perhaps a more difficult task due to its short half-life (7.2 h). The Isotope Program's efforts to form a University network that could provide ^{211}At on regional basis is a potential avenue to alleviate the shortage, and those efforts should continue to have high priority. Alternate methods to produce ^{211}At, such as production of a generator system using ^{211}Rn should be investigated as it could also make a large impact on ^{211}At availability.

Production of ^{225}Ac and ^{211}At can be considered top priority, but production of other alpha-emitters is also important. It is likely that alpha-emitters with different half-lives and daughter emissions may be required for some therapy applications. Production of ^{223}Ra (see Sidebar 3) may be important as a backup supply for commercial sources (Algeta/Bayer) if Xofigo® therapy expands to where the demand outstrips the supply. When producing ^{223}Ra, one obtains another alpha-emitter of interest, ^{227}Th. While the half-life of ^{227}Th ($t_{1/2}$ = 18.7 d) may be considered long for some therapy applications, the fact that it decays to ^{223}Ra makes it attractive for therapy as the clinical effects of the daughter are now known. Production of another alpha-emitting thorium isotope, ^{226}Th is of interest due to the potential for a generator system from ^{230}U ($t_{1/2}$ = 20.8 d) and it decays rapidly (31 min) with 4 alpha emissions to a long-lived beta-emitting daughter, ^{210}Pb ($t_{1/2}$ = 22.3 y). Similar to production of ^{223}Ra, production of ^{224}Ra may be important as a backup to obtain ^{212}Pb/^{212}Bi if the clinical studies being conducted (AREVA Medical) with this in *vivo* generator system are found to be effective in cancer therapy.

β-Emitting Isotopes: Because of the longer particle range, beta-emitting radioisotopes are being investigated for therapy in solid tumors. There are currently shortages of some therapeutic beta-emitting isotopes and/or their theranostic isotope pairs that are of interest in developing therapeutic radiopharmaceuticals. Beta-emitting radioisotopes have been primarily obtained from neutron irradiations of isotopes of the same element in nuclear reactors. While this method of production can provide very large quantities of a radioisotope, the isotope obtained may have a specific activity that is too low or marginal for use in receptor-binding radiopharmaceuticals, as the radioisotope produced cannot be separated from the irradiated target material.

Auger-Emitting Isotopes: As with the alpha-emitting radioisotopes, Auger-emitters hold great potential for future targeted radiotherapies. This is because the Auger electron emissions, while low in energy, deposit that energy in a very short distance, making these emissions high LET. The fact that the Auger electron emissions travel very short distances greatly decreases the normal tissue toxicity relative to that seen with beta-emitting radiopharmaceuticals. Examples of high specific activity Auger-emitters of high interest that have low availability are ^{117m}Sn and ^{77}Br. Research into the production and isolation of high specific activity Auger-emitting radioisotopes should be supported.

The Need for High Specific Activity Radioisotopes

High specific activity (amount of radioactivity per unit mass) is often required for both diagnostic and therapeutic radioisotopes, as non-radioactive impurities, of the same element or of

elements that have similar chemistry, present in the sample have a negative impact on radiolabeling. The radiotracer principle is based on the fact that the mass of the compound administered is below the threshold required to induce a biological response. This is particularly critical when administering radiotracers that are toxic at low doses. Further, the specific activity is important in cases where significant quantities of the isotope are needed in the radio-pharmaceutical dose, and/or there is a need to ship the isotope or radiopharmaceutical containing it over long distances before it is administered. Low specific activity can result in poor targeting of the receptor or antigen that is used to localize the radioactive component in the diseased tissue, making the images uninterpretable or the therapeutic radiopharmaceutical ineffective. High specific activity is also required for theranostic pair radioisotopes used for imaging as a much smaller quantity of the diagnostic radiopharmaceutical may be administered so the diagnostic agent does not alter disease targeting or the pharmacokinetics of the therapy dose.

High specific activity positron or gamma emitting radioisotopes can be produced using accelerators. In many cases the product isotope is a different element than the target isotope and thus can be chemically separated. Development of state of the art radiochemical separation procedures and automated purification systems are often required to ensure the minimization of contamination with non-radioactive impurities. Research in isotope separation science, including the development of automated systems, should be supported to complement the production (targetry) aspects of the work.

Another current area of activity within the Isotope Program is high specific activity beta-emitting radioisotopes made in a reactor using irradiated material different from the isotope being sought. An example of this is reactor production of ^{188}W from ^{186}W, and subsequent isolation of very high specific activity ^{188}Re from decay of the ^{188}W. Additional neutron irradiations of other materials could provide isotopes that are in short supply or have been difficult to obtain at the high specific activity required for therapy. An example of an isotope that has been produced in lower specific activity than desired is ^{67}Cu. ^{67}Cu is a theranostic radioisotope having both gamma emissions that are favorable for SPECT imaging (184 keV) and beta emissions that are favorable for therapy (E_{ave} = 141 keV). Further, it can be used with the theranostic pair positron-emitter, ^{64}Cu, if PET imaging is desired. Another beta-emitting isotope that has been obtained in lower specific activity than desired is ^{177}Lu. Methods are being evaluated for producing both of these isotopes at high specific activity by neutron irradiation of other elements in reactors. Research into reactor methods for producing high specific activity beta-emitters that are in short supply should continue to be supported.

High specific activity beta-emitting radioisotopes can also be obtained from irradiation of other elements by particle beams produced in a cyclotron. Production by cyclotron irradiation may be preferred for many high specific activity isotopes as it is easier to build more cyclotrons if higher production capacity is needed. An example is production of the theranostic radioisotope ^{186}Re. Irradiation of tungsten (W) or osmium (Os) stable isotopes with protons or deuterons can produce high specific activity ^{186}Re. Other high specific activity theranostic radioisotopes in short supply include the beta-emitter ^{47}Sc. All three of these theranostic beta-emitting radioisotopes are of high interest for development of therapeutic radiopharmaceuticals, but availability is low. Research into production routes and isolation methods for high specific activity beta-emitting radioisotopes that are in short supply should continue to be supported.

Human Use Hurdles

Production of diagnostic or therapeutic radioisotopes that will be used in clinical studies must be purified and packaged under carefully controlled conditions. It is absolutely critical that the radioisotope have very high chemical and isotopic purity so that no other chemicals or isotopes are injected which could cause toxicity to the patient. If the radioisotope is used directly as the radiopharmaceutical, the radioisotope must be produced in compliance with FDA current Good Manufacturing Process (cGMP) (21 CFR Part 211 for SPECT and therapeutic radioisotopes, or 21 CFR Part 212 for PET radioisotopes). This can greatly increase the cost of radioisotope production. If the radioisotope is produced as a raw material for use the production of a radiopharmaceutical it can be produced under non-GMP conditions, but complete written records of the isolation, purification and identification must be maintained.

For the production of radiopharmaceuticals used in clinical research studies, it is usually necessary to file an Investigational New Drug (IND) application with the FDA. For the initial Phase 0-1 (and sometimes Phase 2) studies, it is not required to follow the above listed cGMP regulation, but it is required to follow the principles of good manufacturing process. For example, the process must be defined in writing, the components of the manufacturing must be high quality, and segregated from other laboratory chemicals, and written batch records must be used.

Clinical studies assessing the diagnostic utility of several positron emitters are ongoing. In particular radiolabeled antibodies with ^{89}Zr have recently been a very active area of research by both academia and industry. For example ^{89}Zr-trastuzumab studies to assess HER2 expression in both metastatic breast cancer and gastric cancer are ongoing at several sites (see Figure 8). Additionally several companies are using this technique to examine pharmacokinetics of new antibodies in the pipeline as cancer therapeutics.

Clinical studies have been conducted with therapeutic radiopharmaceuticals containing isotopes of all three types of emissions. Clinical studies with beta-emitting radiopharmaceuticals are currently being conducted, and have been conducted over the past 30+ years. As might be expected, one of the major shortcomings of those studies has been the fact that normal tissue toxicity (marrow, liver, kidney, etc.) can be the limiting factor to obtaining therapeutic responses. There are three FDA approved therapeutic radiopharmaceuticals, [^{131}I]Bexxar, [^{90}Y]Zevalin and (^{223}Ra) Xofigo. The first two are highly effective in the therapy of non-Hodgkin's Lymphoma and the latter in prostate cancer. Bexxar has been discontinued as a product, due to lack of commercial success because of competition with several other effective drugs. It seems unlikely this will be the case with other therapeutic radiopharmaceuticals, but that must be evaluated when developing the radiopharmaceutical.

Few clinical studies have been conducted with alpha-emitting radioisotopes. The major concern for getting alpha-emitters into clinical studies is the potential for high toxicity. However, in the multiple studies that have been, and are being, conducted in the U.S. and in Europe, the drugs are well tolerated. Now that an alpha-emitting radiopharmaceutical, Xofigo ($^{223}RaCl_2$) has been approved by the FDA and is being used in clinical practice, it is likely other clinical studies with alpha-emitting radiopharmaceuticals will be able to refer to the low toxicity observed with that agent.

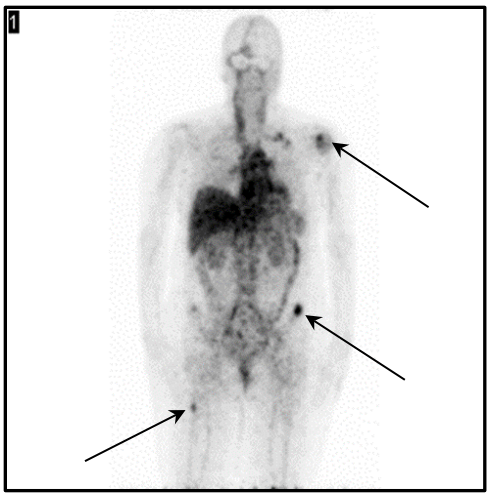

Figure 8: ^{89}Zr Trastuzumab scan in a patient with metastatic breast cancer. There is radiopharmaceutical uptake in lesions in the shoulder, hip, and femur (arrows) indicating positive HER2 receptor expression. *Image courtesy of Dr. Farrokh Dehdashti and Dr. Suzanne Lapi, Washington University in St. Louis*

Radioisotopes for Basic Research

All major pharmaceutical companies make use of compounds labeled with either tritium (^{3}H) or ^{14}C in their drug metabolism and pharmacokinetics groups for metabolism based studies. Tritium-labeled compounds enable the drug developers to perform receptor binding, autoradiography, and receptor occupancy studies. While tritium labeling is relatively easy to perform, the ^{3}H tag is easily removed, *in vivo*. In addition tritium labeled compounds have a modest specific activity which is acceptable for most receptor binding studies and its long half-life (12 y) eliminates the need for a decay correcting data [EL14 and references therein].

^{14}C-labeled material provides the opportunity for use in quantitative whole body autoradiography and mass balance studies, as well as use in human absorption, distribution, metabolism, and excretion studies. During Phase III and beyond, ^{14}C-labeled material is often required for environmental fate studies [EL14 and references therein].

Recommendations

- **We recommend a significant increase of funding for Research and Development**

  Increased R&D is essential for an optimal Isotope Program. Increased R&D is necessary to fully realize the promise of enhanced national security, improved health care, and increased industrial competitiveness the program could provide. It will also support the expansion of the range and quantities of isotopes available for researchers and for potential commercial application, and enhance their usefulness to the Nation. It will support the development of more efficient techniques for their production, reducing costs and ensuring that supplies meet demands. R&D is also a core component of the program, enabling it to better weather fluctuations in revenues (funding) as isotopes transition to the commercial market and as foreign supplies vary. In addition to establishing optimal base R&D funding at the production sites, the increase will facilitate annual (rather than biennial) Funding Opportunity

Announcements (FOAs) to be issued, allowing the program to identify and respond more rapidly to new ideas. This increase will allow the program to effectively support promising new areas as they arise. Two representative areas that would benefit today from increased R&D support are:

- ***Continue support for R&D on the production of alpha-emitting radioisotopes –*** The lack of availability of alpha-emitting radioisotopes was identified in 2009 as a major limitation in the otherwise promising investigations of their potential for cancer therapy. Since the 2009 recommendation, the effectiveness of this novel therapy for cancer treatment has been demonstrated with FDA approval of the alpha emitter ^{223}Ra for metastatic bone cancer from hormone refractory prostate cancer. There has been significant progress made by the DOE Isotope Program in the development and production of some medically useful alpha-emitting isotopes in the past five years, but further research into new production methods, more efficient isolation methods, and automation of the isolation processes is needed to provide adequate availability of alpha-emitting radioisotopes for preclinical and clinical evaluations of this very promising therapy. A focus should continue on production of ^{225}Ac and ^{211}At. In addition, other alpha-emitting radioisotopes that may be applicable for treatment of other types of cancers, or for use in treating bacterial and viral infections are interesting. Thus, research into methods for production/isolation of alpha-emitters with shorter half-lives (e.g. ^{212}Pb/^{212}Bi, ^{213}Bi, and ^{226}Th) and longer half-lives (e.g. ^{227}Th) should also be a priority.

- ***Support R&D into the production of high specific activity theranostic radioisotopes –*** Medical procedures that can be tailored to an individual's unique response will be more effective and lower the cost of health care**.** The move towards personalized medicine will be facilitated by supporting research on the production of radioisotopes, and isotopic pairs of the same element, that have both imaging and therapeutic emissions. Such agents, termed theranostic agents, can be used to obtain valuable pharmacokinetic and disease-targeting information in real time, which can allow rapid determination of whether the therapeutic approach will be effective in a specific patient. A requirement for theranostic radioisotopes produced for medical use is that they have very low quantities of other isotopes of that element present (or "high specific activity") after production and isolation. Personalized medicine will use highly specific targeting of diseased cells in patients to differentiate their disease and help identify treatments that will be effective. High specific activity radioisotopes are required so that the targeted receptor or cell-surface antigen on the diseased cells are bound with targeting agents containing only, or mostly, the theranostic radioisotope. If low specific activity radioisotopes are used, the disease-targeting agent containing a stable isotope (or non-useful radioisotope) can compete for the receptor or antigen, dramatically decreasing binding of the isotope that provides the diagnostic and/or therapeutic emissions. This can lead to inconclusive imaging results and ineffective therapy.

4.B. Research Opportunities with Isotopes in Physical Sciences and Engineering

Isotopes are essential tools in basic research and engineering across a broad range of areas. Indeed, the use of isotopes is finding increased application in diverse trans-disciplinary areas such as energy, materials science, environment and climate change, life sciences and cancer

therapy, space exploration, nuclear waste, and security and monitoring. The preceding chapter provided a glimpse of recent research in some of these areas. In this chapter we discuss some of the new opportunities. Progress in nuclear physics, nuclear structure, and the search for super-heavy elements has been intimately tied to the development and availability both highly enriched and highly neutron-rich projectiles and target isotopes. Further, understanding the fundamental chemistry of trans-uranium and trans-californium elements is pivotal to reaching a possible island of stability for the heaviest elements. Having a sufficient supply of transuranic isotopes would substantially accelerate understanding the chemistry and physics of the trans-uranium elements which, for the first time, is achievable with the modern tools, including a variety of structural, optical, electronic, and magnetic techniques. To assure that intrinsic materials properties are measured high-chemical purity and, if possible, high-isotopic purity are most desirable. To minimize interference in property characterization arising from radiation damage, long-lived isotopes are most advantageous. Curium has electronic attributes (spherically-symmetric ground state, strongly fluorescing excited state) that make it particularly useful to the experimentalist. Similar attributes make it an element of choice for the theorist thus providing a unique opportunity for experimentalists and theorists to collaborate. Magnetic behaviors of some of Cm compounds, including the simple dioxide, are not understood. The isotope of choice is ^{248}Cm, which, although not particularly short lived, is in short supply. This specific isotope is a critical need worldwide.

Waste disposal and the associated environmental contamination is one of the major issues surrounding the Nation's utilization of nuclear energy. With no geological precedent upon which to build, there is a lack of information about even the simplest chemistry of the transuranic elements. The scope of the problem, combined with the difficulties in working with these elements, argues strongly for the development of theories able to predict this very complex chemistry. Establishing the basis for such theories through experimental studies of chemical trends across the actinide series is in the forefront of actinide research.

On the energy front, a fundamental breakthrough could come in the near future: a micro radioisotope thermal generator (RTG) consisting of ^{210}Po embedded in an electronic chip could provide the energy required for operation of the chip. Further work on RTGs could provide high power density for specialized applications.

Neutrinoless double beta ($0\nu\beta\beta$) decay experiments could determine whether the neutrino is its own antiparticle, and therefore whether nature violates the conservation of total lepton number: a symmetry of the Standard Model whose violation might hold the key to the predominance of matter over antimatter. Multiple $0\nu\beta\beta$ experiments using different isotopes and experimental techniques are important not only to provide the required independent confirmation of any reported discovery but also because different isotopes have different sensitivities to potential underlying lepton-number-violating interactions. The most sensitive way to learn about this fundamental nature of the neutrino is to detect these very rare nuclear decays where a nucleus such as ^{76}Ge decays to ^{76}Se by emitting only two electrons (similarly double beta decay of ^{136}Xe to ^{136}Ba , ^{48}Ca to ^{48}Ti, ^{130}Te to ^{130}Xe, and a few others). Next generation experiments will require isotopically enriched samples on the order of 100 to 1000 kg.

Future Isotopes for Use in Physics and Chemistry

During the course of the presentations to the NSACI subcommittee, it became clear that there continues to be a wide variety of uses for isotopes in physical and chemical research as well as a variety of required isotopic purities and quantities. In addition to many areas discussed in the 2009 NSACI Charge 1 report, other opportunities for research involving isotopes were identified by researchers. Examples of research in progress and opportunities enabled by isotopes include:

- Radioisotopes for calibration of neutrino detectors; ^{51}Cr, ^{144}Ce, freshly irradiated Cm targets, fresh HFIR spent fuel, etc. In this specific example, the key challenge is that the magnitude and size of required radioisotopes may require inter-agency agreements, and substantial funds. For example, preliminary calculations indicate that six fresh Cm targets arranged in a flux-trap configuration could provide the highest flux of man-made neutrinos.

- As pointed out in Section 3.B, certain nuclei possessing a large octupole deformation, such as ^{223}Ra and ^{225}Ra, are expected to have greatly enhanced sensitivity to time-reversal violating forces in the nucleus. Experiments using these nuclei are being planned or pursued in a number of laboratories around the world, including Argonne National Laboratory (using ^{225}Ra extracted from a ^{229}Th source at ORNL) and TRIUMF in Canada (using a radioactive beam). The precision of the ^{225}Ra experiment is projected to be limited by the current isotope supply. Based on current estimates, 2-3 mCi of ^{225}Ra is needed every two months for at least two years.

- Isotopes with high isotopic purity required for continued production of superheavy elements and exploration of the island of stability include: ^{233,235}U, ^{237}Np, ^{239,240,242,244}Pu, ^{243}Am, ^{245,248}Cm, ^{249}Bk, and ^{249,251}Cf. Note that with new accelerator facilities with higher beam intensities coming on-line (such as the Super Heavy Element Factory in Dubna, Russia), demand for these isotopes will increase because thicker and larger targets will be required; current targets require ~20 mg whereas future targets are envisioned to require > 100 mg. Note also that high isotopic purity may necessitate usage of an isotope separator capable of separating radioactive material. Isotopes with high isotopic purity required for chemical study include: ^{248}Cm, ^{249}Bk, ^{249,251}Cf, ^{252,254}Es, and ^{257}Fm. The Isotope Program is working with this community to develop a strategic plan for the materials needed for further studies in this area and then to implement it.

- Mixed and mass separated actinides for chemical and physical studies of trans-uranium and trans-neptunium isotopes namely ^{237}Np; ^{242}Pu, ^{244}Pu, ^{243}Am, ^{248}Cm, ^{249}Cf, ^{249}Bk, ^{251}Cf, ^{253}/^{254}Es, and ^{257}Fm. ^{248}Cm is the only readily available isotope of curium that can be used in standard radiochemical facility. The world-wide supply of ^{248}Cm is constrained, and the available ^{249}Bk is currently primarily used as target for synthesis of superheavy elements. ^{249}Bk decays to ^{249}Cf and, similar to Cm, ^{249}Cf is the only Cf isotope readily available that can be used in radiochemical laboratory. Specific metallic and/or chemical forms of these isotopes would be most interesting.

- Very high purity ^{229}Th and ^{233}U for applications in search for the 8 eV γ-ray from ^{229m}Th isomeric transition and as standard reference material for use in mass

spectroscopy of the geological samples to study the distribution of U and Th on the crust of Earth.

- FRIB has the potential to provide increased quantities of ^{225}Ra and ^{223}Ra for atomic electric dipole moments search experiments that would improve the sensitivity by one to two orders of magnitude over what is possible now. FRIB could also allow the search for possible more sensitive candidates, such as ^{229}Pa. FRIB could also provide intense beams of very neutron-rich nuclei that could be used to synthesize more neutron-rich superheavy isotopes. Beams of ^{16}C, ^{17}N, ^{20}O could be used to synthesize very long-lived isotopes of rutherfordium, dubnium, and seaborgium with projected half-lives of longer than one year. This would enable more detailed chemical studies of the heaviest elements.
- To extend fundamental chemistry and physics studies from Cm to Cf, ^{248}Cm and the light transneptunium (^{249}Cf/^{249}Bk, ^{251}Cf, and $^{253/254}$Es) isotopes are needed by the heavy elements chemistry community for use with the modern experimental and theoretical tools that are now available. With recent advances in analytical techniques (including notable developments in the use of synchrotron radiation) a good portion of actinides chemistry and physics studies can be conducted at about the milligram scale. Isotopic purity is sometimes an issue which drives the need for continued optimization of isotope production methods and radioactive isotope separator research and development.
- ^{242}Pu and ^{244}Pu could be extracted from existing stocks of Pu materials that exist throughout the DOE complex and used to support efforts with low activity isotopes and, in particular, support the understanding of materials without radiation damage effects that would be possible with ^{244}Pu.
- Gas and oil exploration requires the continued availability of ^{137}Cs gamma-ray and ^{241}Am/Be sources for logging of wells, and the development of tracers used for tracking extent of deposits, etc. such as ^{131}I, ^{192}Ir, ^{46}Sc, ^{124}Sb.
- Development of RTGs will continue to need isotopes, including lesser used yet developing isotopes such as ^{210}Po, ^{242}Cm or ^{106}Ru.

Planning for Future Isotope Needs Efforts are underway to improve the long-range planning for future needs for isotopes in physics and chemistry. For example, the superheavy element community is working with the Isotopes Program to develop a coherent strategic plan for the field. A similar approach would be useful for the heavy elements chemistry community (coordinated through DOE/BES, which funds most of this work). It is essential that there be feedback to the community after DOE/BES has discussed their needs with the Isotope Program at the annual Federal Isotope Workshop. The end result should be scheduled isotope production "campaigns" with the goals known by the scientists. This would facilitate planning and execution of the experiments (those involving short-lived isotopes such as ^{249}Bk or $^{253/254}$Es require particular attention in this regard). It is also important that there be adequate planning for the costs of these isotopes, both for aligning the expectations of the researchers with the current realities of isotope costs, and for the planning of isotope production by the Isotope Program.

Future Isotopes for Use in Engineering

Route for production of ^{210}Po for applications in micro RTGs: ^{210}Po, which decays with 100% α-particles emission with a half-life of 138.4 days, and with no emissions of γ-rays and neutrons, is the most attractive radionuclide for use in micro RTGs where in some specific applications, the emissions of γ-rays and neutrons are undesirable. Unfortunately, the large scale production of ^{210}Po in a nuclear reactor, which is the primary route for production of this isotope, sufferers from very low yield either due to small cross-section or long half-life of the intermediate radio nuclides as indicated in the reactions 1 and 2 in Table 7. Consequently, large scale production of ^{210}Po in a nuclear reactor is inherently bulky and expensive. Production of ^{210}Po in an accelerator using α-induced reactions (reactions 3 and 4, Table 7) is also inadequate. In this case, although the reaction cross-sections are relatively large, insufficient target cooling limits the target thickness resulting in limited production. There is currently no domestic production of ^{210}Po in U.S., however, Curie quantities of this isotope are available from Russia.

Table 7: Routes for production of ^{210}Po

No.	Nuclear Reactions	Comments
1	$^{209}Bi[n,\gamma]^{210}Bi(\beta^-, t_{1/2}=5.0d)^{210}Po$	Low yield due to small cross-section
2	$^{208}Pb[n,\gamma]^{209}Pb$ (β^-, $t_{1/2}$=3.3 h) $[n,\gamma]^{210}Pb(\beta^-, t_{1/2}=22y)^{210}Po$	Low yield due to large $t_{1/2}$ of ^{210}Pb
3	$^{208}Pb[\alpha,2n]^{210}Po$	Low yield due to limited target thickness and cooling requirement
4	$^{209}Bi[\alpha,3n]^{210}At(EC, t_{1/2}=11 h)^{210}Po$	Low yield due to limited target thickness and cooling requirement

The isotopes with identified research opportunities and research applications (discussed in section 3B) are listed in Table 8. In particular, cases are listed where a shortage or potential shortage of isotope supply is an issue. The table is ordered by rough priority in the physical sciences and engineering areas. The prioritizations are based on the subcommittee's expertise and the priorities presented to NSACI from the DOE-NP and DOE- BES programs.

Table 8: Research opportunities in the physical sciences and engineering where a shortage or potential shortage of isotope supply is a challenge

Research Activity and Applications	**Isotope (half-life)**	**Challenge/Action**
Operate the CARIBU facility at ANL to produce and study radioactive beams of nuclei from ^{252}Cf fission for research in nuclear physics and astrophysics.	^{252}Cf (2.6 yr)	Limited supply of ^{252}Cf; 1 Ci source is needed each 1.5 year for at least for four years.
Measurement of permanent atomic electric dipole moment of ^{225}Ra and ^{223}Ra to search for time reversal violation, proposed to be enhanced due to effect of nuclear octupole deformation.	^{225}Ra (15.0 d) ^{223}Ra (11.4 d)	Supply of ^{225}Ra is limited. 2-3 mCi of ^{225}Ra is needed every two months for at least two years.
Create and understand the heaviest elements possible, all very short lived and fragile. Produce very neutron-rich target isotopes for these studies.	^{244}Pu (8.0x10^{7}y) ^{248}Cm (3.4x10^{5}y) ^{247}Bk (1.4x10^{3}y) ^{249}Bk (320 d) ^{254}Es (276 d)	Produce certain actinides in HFIR, and then prepare targets for accelerator-based experiments to make super-heavy elements. Need 10-100 mg on a regular basis and purity is important. Plan for mass separation of these radioisotopes.
Study the atomic physics and chemistry of actinides and heavy elements for basic research, advanced reactor concepts, environmental behavior, and nuclear waste disposition.	^{209}Po (102 y) ^{229}Th (7.9x10^{3}y) ^{231}Pa (3.3x10^{4} y) ^{237}Np (2.1x10^{6}y) ^{244}Pu (8.0x10^{7}y) ^{248}Cm (3.4x10^{5}y) ^{247}Bk (1.4x10^{3}y) ^{249}Bk (320 d) ^{254}Es (276 d)	Plan for production of these isotopes in HFIR. Similarly, plan for mass separation of these radioisotopes.
Standard reference material for isotope dilution mass spectrometry applications, and spikes for mass spectrometers	^{229}Th (7.9x10^{3}y) ^{233}U (1.6x10^{5}y) ^{236}Np (1.5x10^{5}y) ^{236}Pu (2.86 y) ^{244}Pu (8.0x10^{7}y) ^{243}Am (7.4x10^{3}y) ^{202}Pb (5.3x10^{4}y) ^{203}Pb (51.9 h) ^{205}Pb (1.5x10^{7}y) ^{206}Bi (6.24 d) ^{210}Po (138.4 d)	Isotopes for Standard Reference Materials that are not produced by the Isotope Program are in limited supply; high purity ^{236}Np is not available; 10-100 mg needed on annual basis; high purity is essential. ^{202,205}Pb difficult to obtain in high purity in gram quantity.
Search for double beta decay without neutrino emission – an experiment of great importance for fundamental symmetries.	^{136}Xe → ^{136}Ba ^{130}Te → ^{130}Xe ^{48}Ca → ^{48}Ti ^{76}Ge → ^{76}Se	Large quantities of highly enriched isotopes are needed for the fabrication of large detectors. U.S. does not have the capability to produce the ~1000 kg quantities needed.
Avogadro international project – weight standard based on pure ^{28}Si crystal balls.	^{28}Si (stable, nat. abundance 92.2%)	Concern about future supply and cost of kg quantities of this material, which is currently available only from Russia.
Radioisotopes micro-power source.	^{147}Pm (2.62 y) ^{210}Po (138.4 d) ^{238}Pu (87.7 y) ^{244}Cm (18.1 y)	^{147}Pm and ^{210}Po are available only from Russia. Development needed for efficient conversion.
Isotopes for Mössbauer spectroscopy, over 100 radioactive parent/stable daughter isotopes.	^{57}Co, ^{119m}Sn, ^{67}Ni, ^{161}Dy, …	The majority of isotopes used in Mössbauer spectroscopy are currently available only from Russia – a concern for scientific community.

Recommendations

Among the major recommendations we are making, one that will have specific impact on R&D in the Physical Sciences and Engineering is:

- **We recommend an increase in the annual appropriated budget to realize the opportunities associated with high-impact infrastructure investments and to maintain a stable funding base for reliably operating and continually improving facilities. Specific opportunities for the period covered by this Long Range Plan include:**

  - ***Infrastructure for isotope harvesting at FRIB*** **-** During routine operation for its nuclear physics mission, FRIB will produce a broad variety of isotopes that could be harvested synergistically without interference to the primary user. Research quantities of many of these isotopes, which are of interest to various applications including medicine, stockpile stewardship and astrophysics, are currently in short supply or have no source other than FRIB operation. The technical and economic viability of this proposed capability should be developed and assessed promptly.

Promising research opportunities in the physical sciences and engineering that should be investigated include:

- To extend fundamental chemistry and physics studies from Cm to Cf, renew production of ^{248}Cm, and make the light transneptunium (^{249}Cf/^{249}Bk, ^{251}Cf, and $^{253/254}$Es isotopes) more available and affordable to the heavy elements chemistry community so that they can be more fully used with the modern experimental and theoretical tools that are now available. With recent advances in analytical techniques (notable developments in the use of synchrotron radiation) a good portion of actinides chemistry and physics studies can be conducted at about the milligram scale, and the sensitivity of the techniques is expected to remain at this level over the next 10 years. That said, these isotopes are often cost-prohibitive, and efforts to lower their costs would greatly facilitate the research.
- Develop capabilities to isolate ^{242}Pu and ^{244}Pu from existing stocks of Pu materials that exist throughout the DOE complex (primarily at LANL) that can be used to support efforts with low activity isotope and, in particular, support the understanding of materials without radiation damage effects that would be possible with ^{244}Pu.
- To undertake scheduled campaigns, with the prior knowledge of the scientific community, such that experiments using specific short-lived isotopes (e.g. ^{249}Bk or $^{253/254}$Es) could be planned and executed.

4.C. Research Opportunities with Isotopes for National Security and Other Applications

The major applications of isotopes in national security relate to their use in the development and implementation of radiation detection applications, certification of analytical techniques used in destructive analysis of nuclear and radiological materials, and nuclear physics research intended

to improve and verify the fidelity of nuclear explosion codes. A number of factors drive the need for continued research in these areas.

Research in the use of isotopes is often driven by the need for production of or replacement of scarce materials, and there is new interest in the means for production or mining of important isotopes. The availability of new experimental facilities is also opening avenues for research that will greatly benefit from the availability of isotopes.

Radiation detection

Limitations on the availability of ^{3}He traditionally used in the manufacture of neutron detectors used in radiation portal monitors has led to interest in the use of replacement isotopes as conversion materials. Several technologies have been evaluated for this purpose, including the use of boron-lined or BF_3-based proportional detectors or detectors (in which ^{6}Li is coated on or embedded in scintillating glass fibers). While each has tradeoffs in cost and robustness, all technologies fundamentally meet the requirements of sensitivity and gamma discrimination, and several agencies have undertaken acquisition of these alternative systems [GAO11].

Research is ongoing to explore several additional alternatives for both portal monitors and smaller, more portable detector applications. Approaches vary, from the development of new scintillator materials to the development of semiconductor based technologies. Many of these rely on the incorporation of standard conversion materials (^{10}B, ^{6}Li) into the detector material; gadolinium (natural abundance or ^{157}Gd) is less commonly used due to its reduced gamma discrimination capability. This research will continue to drive interest in the availability of ^{6}Li. The Isotope Program coordinates with NNSA to transfer (and subsequently purify) sufficient quantities of ^{6}Li to accommodate expanded research with this isotope. This path should be adequate to ensure a stable supply.

Analytical and radioanalytical methods

The increase in application of radioanalytical chemistry in nuclear security (in missions such as forensics and environmental safeguards) creates a need for reference materials and calibration standards. While the Isotope Program does not provide the reference materials and calibration standards directly, it does provide the isotopes needed to produce them. It is a very positive sign that the Isotope Program has become engaged in planning with this community. As reported by the National Technical Nuclear Forensics Center, representatives have engaged with the Isotope Program, both directly and through the Federal Isotope Workshop. This interaction can be informed by the results of a series of interagency workshops that have taken place to evaluate the needs for new directions for reference materials certified to support laboratory quality envelopes, as well as support laboratory intercomparisons and proficiency exercises [IN08, IN13].

More unique isotope needs exist in requests for other types of reference materials, such as isotope dilution standards, and radiochronology reference materials (see Sidebar 8). For the most accurate quantitative analysis, both alpha spectrometry and mass spectrometry methods require an isotope dilution tracer for each element. Current needs identified in this area include standard solutions of ^{229}Th, ^{233}U, ^{236}Np, ^{244}Pu, and ^{243}Am for Isotope Dilution Mass Spectrometry (IDMS) (certified for mass content), and ^{236}Pu for alpha spectrometry (certified for activity).

Sidebar 8: The value of isotopic standards in nuclear forensic analysis

The field of "nuclear forensics" is the scientific analysis of nuclear or other radioactive material, or of evidence contaminated with radioactive material (such as the one shown in Figure 9), for the purpose of determining its origin. As is the case in any forensic investigation, the value of the information derived from such analyses rests on the demonstration of the reliability of the methods through the accurate reproducibility of the analysis procedure [LE09]. A number of material characteristics may be of interest in any investigation, including the physical and chemical form of the sample, as well as isotopic signatures that are created by the history of its production, separation, processing, and age. For this reason, precise measurement of the *isotopic* constituents of the materials is a necessary aspect of this evaluation.

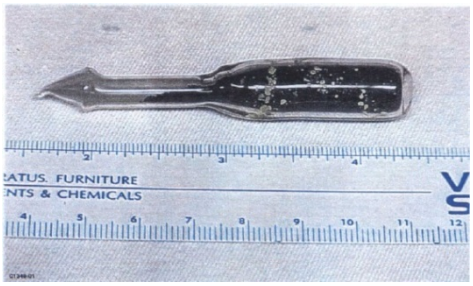

Figure 9: Determination of the characteristics of an unknown interdicted sample often relies on isotopic measurements and certified isotope reference materials. The glass ampule shown (interdicted in Bulgaria) was determined to contain highly enriched ^{235}U

Certain measurements rely on the availability of well-characterized isotopic standards. One example is the use of isotope standards for quantifying amounts of radionuclides by a method known as Isotope Dilution Mass Spectrometry (IDMS). Mass spectrometry is a method in which the chemical and isotopic compositions of samples are determined by measurement of their mass. In the IDMS method, a known amount of an isotopically enriched standard (a "spike" - using an unusual isotope of the element to be measured) is added to the unknown. By subsequent measurement of the ratio of isotopes, it is possible to determine the quantity of radionuclide in the original sample with great precision. In addition to measurement of the absolute quantities of materials, sensitive isotopic measurements support other forensic conclusions. For example, radiochronometry is a measurement often used to determine the age of a material. A radioactive material (the "parent") decays to other elements/isotopes ("daughters") at known decay rates. By measuring the ratio of parent-daughter pairs, it is possible to calculate the time that has elapsed since the sample was chemically separated.

In order to demonstrate the validity of a method, particularly if the information will withstand legal scrutiny, the analysis must be carried out within a quality system that includes demonstration on appropriately certified reference materials. The particular needs of nuclear forensics therefore create a demand for small quantities of specific isotopes often with high isotopic purity for the production of these reference materials.

In recent years, international dialog and cooperation in nuclear forensics has grown significantly [IA14]. The need to establish the comparability of measurements between different laboratories (and improve confidence in the conclusions based on these measurements) often relies on the conduct of inter-comparison exercises, employing certified standards as samples. This is expected to increase the need for certified reference materials.

Although ^{242}Pu is available as an IDMS tracer, it is not the ideal choice for these applications. ^{242}Pu can be an important analyte in trace plutonium measurements (and likely to be more important in safeguards applications as advanced fuel cycles begin operation). Another identified need is for neutron-deficient lanthanide tracers (^{148}Eu, ^{149}Eu) to study lanthanide separations. The generation of many reference materials is hampered by a lack of parent domestic supplies of high enrichment and pure isotopes.

The Isotope Program has begun to work with other agencies in meeting these needs. For example, a project has been funded at LANL (in a collaboration with the University of Washington) to explore accelerator-based production of ^{236}Np and ^{236}Pu. This is a positive trend; we encourage continuation of these collaborations to make progress on urgent needs.

Radiochronometry measurements also require standards. Identified needs exist for reference materials associated isotope ratio pairs, including ^{234}U/^{230}Th, ^{235}U/^{231}Pa, and ^{236}U/^{232}Th (for age-dating uranium-containing materials), as well as ^{238}Pu/^{234}U, ^{239}Pu/^{235}U, ^{240}Pu/^{236}U, and ^{241}Pu/^{241}Am (for age-dating plutonium-containing materials). Among the highest priority reference material needs are ^{137}Cs-^{137}Ba and ^{235}U/^{231}Pa radiochronometric reference material; planning and evaluation is underway in programs funded through the Domestic Nuclear Detection Office (DNDO) for some of these standards.

Although there is no production-scale mass separator available to the Isotope Program for radioactive isotope separation, Idaho National Laboratory (INL) is in the final stages of developing a research-scale radioactive mass separator. INL currently runs a stable mass separator (funded by the FBI and DHS) to produce high purity materials at modest (mg) levels [CA13] for DNDO's National Technical Nuclear Forensics Center (NTNFC). After the purity and quantity/activity of these isotopes have been verified, they are provided as CRMs to the nuclear forensics community. This effort demonstrates the utility of radioactive mass separation capability for the production of high purity isotopes. These applications support the recommendation to develop a strategy for the re-establishment of a separator for radioactive isotopes to support research (recommendation 3b). The radioanalytical community has also identified a need for low isotopic purity materials that could be used in this mass separator to generate additional priority standards, such as ^{84}Sr and ^{96}Zr for use in radiochronometry reference materials.

Nuclear physics research for national security applications

Understanding the myriad of reactions that occur in the high neutron fluence of a nuclear explosion (and attendant radiation and particle transport) is important to informing performance models, and to interpreting the radiochemical signatures used in the characterizing events during the U.S. underground nuclear test program. Weapons radiochemistry as an interpretive tool relies on accurate nuclear data; it is used to inform the models created to interpret the complicated elemental and isotopic signatures that arise in debris. Nuclear science (both theory and experiment), therefore, supports both the underlying physics associated with explosion codes and the refinement of diagnostics that are used increasingly in the validation of models against test history. Research needs exist both to incorporate new data, and to reduce uncertainties associated with known parameters such as reaction cross sections, decay constants, and isomeric effects. The implications of this understanding extend to other missions in national security. As

discussed previously, forensic investigation of nuclear events rests on the technical capabilities developed in weapons applications. Radiation detection applications in nonproliferation and emergency response efforts also rely on accurate (and precise) nuclear data; evaluated data in nuclear data libraries informs radiation transport codes such as MCNP or GEANT that are important to sensitive detection and high precision assays. With the spectrum of current (and emerging) facilities for nuclear science, the opportunity exists to provide important data and improve the fidelity of models of nuclear processes.

The neutronics environment of a nuclear explosion is complex. Fission and fusion reactions are accompanied by the subsequent interaction of neutrons with debris through capture, scattering and fission reactions. Data must inform both models of the primary energy-producing reactions, and account for observed radiochemistry data measured on debris, including the results associated with the use of radiochemical detectors. Research needs can be identified in each of these areas. Work is ongoing to address needs for accurate data (including fission product yields, total kinetic energy, and the energy distribution of fission neutrons, as a function of incident neutron energy) associated with fission in nuclear fuels, particularly plutonium.

Data is also needed for the evaluation of neutron capture reactions in the 1 keV to 2 MeV energy range. There are several reasons why an understanding of these nuclear processes is vital, including improving the interpretation of radiochemical detectors. Experimental efforts addressing these data needs would clearly benefit from access to isotopically pure radioactive targets of isotopes such as ^{73}As, ^{88}Y, and ^{88}Zr-, as well as isotopes of Eu, Tm and Lu.

While many neutron reaction cross sections on isotopes used as detectors are adequately known, higher-order reactions can occur. In a nuclear device the neutron fluence is sufficiently high that multiple reactions can occur on a single atom. Often these are sequential reactions from the ground states of adjacent isotopes, but the total neutron exposure time in a nuclear device is sufficiently short that the second order reactions can occur on not only the ground state of the isotope but, in some instances, on an excited state of the isotope (or isomer). The cross sections for reactions on these excited states are experimentally unknown and are, to date, dependent on nuclear modeling.

In some cases, it may be necessary to evaluate nuclear reactions associated with very short-lived species (e.g. fission products). In such cases, it is desirable to have the capability for in-beam experiments, using radioactive ion beams. In other cases, it is necessary to evaluate nuclear decay processes in detail to provide constraints to theories used to calculate reactions on short-lived isotopes, such as utilizing beta-delayed neutron emission in traps to inform neutron capture reactions.

A new generation of experimental facilities is providing the motivation to propose the studies that will require access to research quantities of isotopes. Other facilities are providing the opportunity to access these isotopes. Smaller laboratories are critical for the training of students. Several facilities have been used by national security programs over the past decade to conduct nuclear science experiments, including facilities at national laboratories (such as the Los Alamos Neutron Science Center, or LANSCE) and universities (e.g. the Triangle Universities Nuclear Laboratory at Duke University and the Laboratory for Laser Energetics at the University of Rochester). The proximity of nuclear science experimental capabilities at LANSCE to the

LANL Isotope Production Facility provides intriguing opportunities for the production and use of radioactive targets. New (or reconstituted) facilities create new opportunities for experimental scientists. After a hiatus of several years, the U.S. has recently resumed operation of a general-purpose critical assembly experimental facility, NCERC (National Criticality Experiments Research Center). The NCERC is located at the Nevada National Security Site and operated by LANL, and provides access to relevant fission-spectrum irradiation capabilities. LLNL operates the National Ignition Facility (NIF), designed to create temperatures and pressures (and fusion-spectrum neutrons) similar to those that exist in nuclear weapons. This facility provides the opportunity to study plasma coupling to nuclear excitation and decay processes.

For very short-lived species, the Facility for Rare Isotope Beams (FRIB) at Michigan State University will provide the opportunity to examine in-beam reactions [BO10]. An example of the utility of this capability would be evaluation of neutron-induced reaction rates associated with production and destruction of fission products for A=95 (near one of the peaks in the fission product distribution curve). The cross sections of interest are shown in Figure 10. Generation of a ^{95}Sr beam at FRIB, coupled with developments of inverse kinematics reactions such as (d,p) reactions, will enable experimental determination of a few key cross sections and improve the theoretical models used to calculate other reactions and cross sections [LL15].

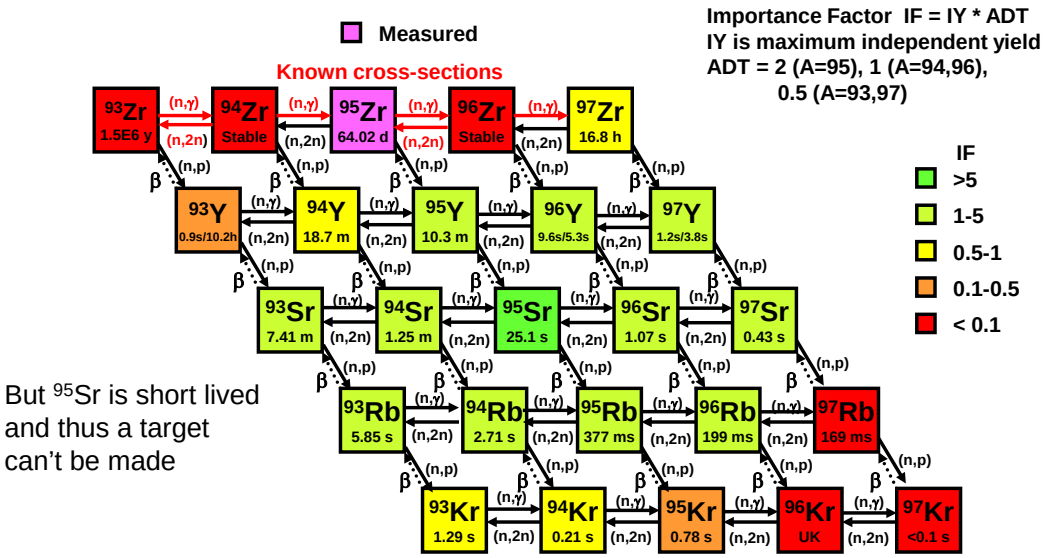

Figure 10: Key reaction cross sections near A=95

FRIB also presents a new opportunity to access a broad range of radioactive isotopes through isotope harvesting (see Section 6.D.). Specific opportunities have been identified, including harvesting ^{48}V or isotopes of europium in the range ^{147}Eu-^{154}Eu. These opportunities support consideration of the infrastructure for isotope harvesting at FRIB.

Other Areas of Research

Other areas of R&D that may lead to new applications range from multi-isotope ring laser gyroscope development in inertial navigation systems to nuclear battery technology (alpha- and betavoltaics). Undoubtedly, new opportunities will arise that impact needs in the national security arena. The Isotope Program provides a vital service in supporting access to a wide range of research utilizing isotopes, and should continue to find opportunities at the core production sites and universities to enable exploration of production routes through a vital and diverse research program.

Chapter 5: The Scope and the Scientific/Technical Challenges for the Isotope Program

The previous chapters have outlined the importance of isotopes to the Nation and the key role of the DOE Isotope Program. The isotopes it supplies enable the U.S. to be at the forefront of science and innovation. Moreover, the Program is the source of expertise that assists in the production of isotopes for Federal missions and the U.S. isotope industry. It works with multiple government agencies including DOD, NNSA, Department of Homeland Security, Bureau of Land Management, U.S. Geological Survey, DOE Office of Science NP and BES, NIM, National Technical Nuclear Forensics Center, NIST, NASA, to name a few, to anticipate and meet their isotope needs. The breadth and importance of this program leads to significant challenges that must be addressed as its reliability and health is crucial for the long-term ability of the U.S. to lead developments in medicine, basic physical and biological sciences, national security and industry.

Scope and Mission of the Isotope Program

The central role that isotope availability plays in government, academe, and industry requires that the Isotope Program ensure a supply of critical isotopes, as they are needed. The scope of the facilities and/or specialized workforce required to produce these isotopes normally precludes their supply by industry, yet they can be provided as a byproduct of the basic research supported by the DOE Office of Science. The program mission was established in recognition of the opportunities and challenges inherent in ensuring a reliable supply.

The mission of the DOE Isotope Program is threefold:

- Produce and/or distribute radioactive and stable isotopes that are in short supply, associated byproducts, surplus materials, and related isotope services;
- Maintain the infrastructure required to produce and supply isotope products and related services; and
- Conduct R&D on new and improved isotope production and processing techniques which can make available new isotopes for research and applications.

Meeting the mission requires that the Program anticipate the isotope needs of its clients and ensure that the necessary tools and workforce exists to respond. It requires that the program have sufficient resources to support the infrastructure and R&D critical to production, distribution, and improvement. The R&D part of the mission is particularly important to enable the Program to anticipate and respond to changes in demand and need. For example the great potential of alpha-emitters for cancer therapy can only be realized if a range of alpha-emitting isotopes are available for the necessary clinical trials. Corresponding maintenance and upgrades of the production infrastructure are necessary to keep the facilities healthy. Ultimately, increases in the supply of isotopes are made possible by further investments and expansion of the production facilities.

The DOE Isotope Program does not compete with commercial isotope production, but does in many cases provide industry with a reliable supply of key isotopes. The unique capabilities of high-flux reactors, high-energy particle accelerators, and research infrastructure that exist within the U.S. laboratory system provide a capability for isotope production that does not exist elsewhere. An example is the case of ^{32}Si, which is important for climate change research, yet is

very difficult to produce and relies on the high-energy accelerator facilities available to the Program. The Program must coordinate the isotope production capabilities that exist within the DOE complex and work with universities to fill the needs for isotopes. Only after the demand for specialized isotopes is demonstrated over many years might industry invest in the substantial resources needed to join production. As commercial sources become available the program moves to production of other isotopes as they grow in demand.

Key Challenges

The challenges to the program are significant; it must respond to the needs of many and varied entities. To be effective, it must maintain broad and expensive accelerator, reactor, and radiochemical capabilities. Many of these capabilities require highly trained teams with unique expertise that cannot be easily replaced. The production facilities operate parasitically to facilities that are run for other purposes and the program must respond to breaks in production and running schedules that are set by other considerations. Many radioisotopes must be used within hours or days of their production, and yet medical treatments require stable long-term availability. An interruption in supply can lead to unrealized potential of a promising new application.

To work well, all customers and especially federal agencies must accurately project their needs, and the Department of Energy must coordinate these requests and provide feedback on actual availability. For example, the National Cancer Institute does not want to fund medical research for isotopes that will not be available, but DOE cannot plan to produce these isotopes in quantity unless they are aware in advance what isotopes and what quantities are needed. Often foreign suppliers are heavily subsidized and it is difficult for the U.S. to maintain or develop domestic production of critical isotopes. Yet foreign supply can be unreliable as was demonstrated in the case of ^{99}Mo supply interruption (see Sidebar 9). Transportation of radioactive isotopes remains a significant issue. Regulatory changes can have tremendous cost implications on the producers and can threaten the ability to supply isotopes critical for medical diagnostics.

Since 2009 the program has successfully tackled many of these challenges and most of the concerns raised in the previous Isotope Long Range Plan Report have been addressed. The program has established effective lines of communication with agencies, the research community and industry to better respond to and anticipate needs. The lack of a continuous supply due to the running schedules of the production facilities has been addressed by close coordination of facilities by the Isotope Program and by making investments to ensure that at least two running facilities able to respond to the needs. Incorporating university labs and foreign resources has expanded the network of suppliers.

Isotope demand may change significantly from year to year, e.g., a shift to commercial suppliers or by the emergence of a new application. The program has put in place a strategic planning process that considers the demand for each isotope and the likely future changes. A critical step since the 2009 LRP is that the program has established an effective R&D program. R&D is critical to develop new isotopes and new production techniques, to ensure the improved availability of isotopes that will be needed in the future. The lead-time for development of an isotope can be long and it is clear that increased research funds are needed. While the existing

Sidebar 9: ^{99}Mo, a Status Report

Technetium-99m (^{99m}Tc) is the most widely used radionuclide in nuclear medicine throughout the world. Approximately 85% of all nuclear medicine scans use ^{99m}Tc. That amounts to >35,000 scans/day in the United States (approximately 1 scan/second) or 10 – 20 million doses/year [PI13, LO12,WI09]. The ^{99m}Tc is obtained from a generator containing ^{99}Mo which decays to ^{99m}Tc. The fission of ^{235}U provides ^{99}Mo in very high specific activity, which is required for the ^{99m}Tc generators that are currently being used.

Until about 2010 the majority of the supply was provided by five multi-purpose research reactors owned and operated by their respective governments. At that time, the National Research Universal reactor (NRU) in Canada and the High Flux Reactor (HFR) in The Netherlands supplied approximately 70% of the world demand and the remaining three reactors (Safari in South Africa, BR2 in Belgium and Osiris in France) combined to make up the difference. All are more than 3 decades old with two having been built over 50 years ago, and all made use of Highly Enriched Uranium (HEU). In spite of the efforts by the respective teams to maintain the infrastructures, the two oldest reactors have gone through a series of unanticipated interruptions. There was a period when both were unavailable for ^{99}Mo production for more than 6 months and a period in 2010 when at least one had not been operational for more than a year [GC14].

Since that time two existing European research reactors, the Maria reactor in Poland and the LVR-15 reactor in the Czech Republic have been added to supply ^{99}Mo. The new OPAL reactor in Australia began irradiating low enriched uranium (LEU) targets to produce ^{99}Mo in 2003. The five commercial ^{99}Mo producers utilizing those eight reactors for the production of ^{99}Mo have provided a much more robust and reliable supply of ^{99}Mo since 2010. This has been evidenced by the industry supplying ^{99m}Tc generators even during periods when multiple reactors were down for maintenance.

As was the case at the time of the 2009 NSACI report, the National Nuclear Security Administration (NNSA) at DOE is responsible both for overseeing the elimination of civilian uses of ^{235}U (to reduce the threats associated with the potential use of highly enriched uranium HEU, for nuclear weapons) and for improving the reliability of the U.S. domestic supply of ^{99}Mo. As part of the NNSA effort to address these responsibilities, several entities made proposals for alternative production of ^{99}Mo without the use of HEU. There are two active Agreement partners with three projects in the U.S.:

1. the neutron capture ^{98}Mo(n.γ) reaction is being pursued by *NorthStar* using the Missouri University Research Reactor (MURR) for the source of neutrons. MURR first produced ^{99}Mo via this method more than 3 decades ago; *NorthStar* is also exploring the inverse ^{100}Mo(γ,n) reaction, using photons produced using a 35-50 MeV high intensity electron accelerator; and
2. use of a sub-critical solution reactor driven by neutrons from a (d,t) accelerator is being pursued by *SHINE,* which is based in Wisconsin.

The two *NorthStar* approaches yield low specific activity ^{99}Mo not suitable for the existing fission based generator system. A new type generator has been developed and is under review for approval from the FDA for use in the clinical setting. The *Shine* project is still in the

Sidebar 9 (cont.)

development stages because the accelerator requires very high fluxes of neutrons (and thus very high beam current from the deuteron accelerator), and the solution reactor also has a significant licensing lead time.

The international community is also investigating alternative approaches. For example the Canadian government is sponsoring three efforts: two are based on the use of low energy cyclotrons (16-24 MeV) producing ^{99m}Tc directly, while the third is pursuing the ^{100}Mo(γ,n) reaction, which produces low specific activity ^{99}Mo. The International Atomic Energy Agency is sponsoring a cooperative research program to assist Member States with developing the cyclotron approach for their respective needs. A number of reactors have been proposed including the replacement for the Dutch reactor (PALLAS) but the time line is at least a decade from 2015. The French Jules Horowitz reactor has been delayed. A number of other existing reactors are being considered as potential sources of ^{99}Mo. Of the reactor approaches, the upgrade of the OPAL reactor in Australia has the greatest possibility of impact. Once the OPAL facility is upgraded, they are expected to increase their weekly production of ^{99}Mo from 1,000 Ci to 3,500 Ci. The FRM2 reactor in Munich is also being examined another facility capable of irradiating targets for ^{99}Mo production, as well as the new Jules Horowitz reactor in Cadarache, France.

An important aspect of the ^{99}Mo situation is the push from the Organisation for Economic Co-operation and Development (OECD) to establish the production at full cost recovery. Without full cost recovery it will be difficult for new suppliers to penetrate the market. The ^{99}Mo situation has been reviewed recently by both the U.S. and Canadian governments and the International Atomic Energy Agency (IAEA) [GC14, IAEA13, NSAC14]. As discussed in Chapter 3, the NRU reactor is expected to stop routine irradiation of ^{99}Mo targets in 2016. Although there is reason for optimism, the excess production capacity of ^{99}Mo will be reduced slightly between 2016 and 2018 because of the NRU reactor.

R&D program is a success, currently not all high-priority research can be funded within the funds available. R&D programs at the production sites are also critical for long-term viability of the program, and the current R&D level at all the production sites is below optimal levels. Production sites can easily become fully occupied meeting customer demand and then be unable to support new innovations or the evolution needed to meet changes in demand. R&D is required to develop solutions to meet demand based on improvements in production techniques. Scaling up production and optimization of extraction for new isotopes also requires R&D investments.

The challenge of sole-source foreign supply remains a problem (see Sidebar 10). The program has addressed this by the reestablishment of the stable isotope program, as recommended in the 2009 LRP. Yet, the critical supply of certain isotopes still relies on foreign sources. Continued investments are needed for aging infrastructure to modernize and increase reliability and efficiency. A base funding level for modernization must be maintained so that when a disruption in foreign supply occurs, the U.S. program can move quickly into production.

Sidebar 10: Foreign Supply of Key Isotopes

While the U.S. produces a significant number of the isotopes used by researchers, industry and the medical community, the U.S. is dependent upon foreign sources for many. Historically the U.S. provided almost all of the isotopes that were required for domestic consumption or, in special cases, acquired them from long-time allies. But beginning in the 1990's other governments began to view the isotope industry as a high tech growth industry, and subsidized the production and sale of isotopes, targeting U.S. companies. The result is that U.S. industry has been switching its buying from the U.S. and DOE to foreign sources of supply. The most aggressive of these foreign countries has been the Russian Federation. This change in purchasing behavior has resulted in the discontinuation of production of many critical isotopes by U.S. producers and by the DOE Isotope Program. The subcommittee has identified at least 40 different isotopes that are only produced outside of the U.S.. The most important of these is ^{99}Mo, but there are many other very important isotopes on which the U.S. is dependent on foreign supply. A sampling of the most important of these includes:

ISOTOPE	Use
^{241}Am	Industrial – Smoke Detectors, Oil & Gas Exploration, Road Construction
^{133}Ba	Industrial – Oil & Gas Exploration, Homeland Security, Flow Measurement
^{14}C	Medical – Radio labeling of drugs; Industrial – Environmental Monitoring
^{109}Cd	Industrial – X-ray Fluorescence for Material Analysis
^{57}Co	Medical – Gamma Camera Calibration; Industrial – X-ray Fluorescence, Nuclear Fuel Rod Examination
^{60}Co	Medical & Industrial – Radiotherapy & Sterilization
^{137}Cs	Medical & Industrial – Sterilization, Oil Exploration, Road Construction
^{55}Fe	Industrial – Chemical Analysis
^{153}Gd	Medical – Medical Scanner Calibration
^{125}I	Medical – Brachytherapy
^{90}Sr	Industrial – Aerospace (Strain & Fracture detection), Gauging & Measurement

The DOE Isotope Program or other domestic manufacturers produced some or all of these isotopes in the past. While it is not expected that the U.S. will be able to develop sufficient capacity in the production of these isotopes to eliminate foreign sources of supply, a domestic capability to produce limited quantities or stockpile would act as a hedge against possible disruption. This is a topic that the DOE Isotope Program has begun investigating recently.

World Production of Key Stable Isotopes: The largest suppliers of stable isotopes, accounting for the majority of stable isotopes produced worldwide are URENCO (Netherlands) and the five Russian production sites managed by Russian Federal Atomic Energy Agency (ROSATOM) and the Kurchatov Institute.

Based in Almelo, Netherlands, URENCO Stable Isotopes has been a top world supplier since 1990. Employing centrifuge technology, URENCO produces a broad range of isotopes (including isotopes of C, Ti, Cr, Ni, Zn, Si, Mo, Cd, Ge, Se, Kr, W, Ir, Te, Xe) used in medical diagnostics and brachytherapy, as well as industrial applications. The company asserts it can produce stable isotopes from an additional 15 elements, as required. URENCO is the leading world supplier of ^{64}Zn, commonly used as moderator in power plant cooling circuits. Russian production of stable isotopes essentially occurs at five production sites in Siberia and the Ural Mountains, and is claimed to account 40% of the world's production. However, their infrastructure is heavily dependent on older electromagnetic separation technology (calutrons).

Sidebar 10 (cont.)

ROSATOM intends to upgrade and expand gas centrifuge technology for isotope separation by 2018, and will focus particularly on the production of stable isotopes needed in the nuclear medicine community, including $^{142\text{-}150}$Nd, $^{162\text{-}170}$Er, $^{152\text{-}160}$Gd and $^{168\text{-}176}$Yb. The combined Russian catalogue of "available" stable isotopes is exceptionally broad, and Russia remains the first stop in any search for "difficult-to-source" isotopes. Production of stable isotopes in other countries is primarily limited to ^{18}O water and gas for the medical community (PET applications), notably in Israel and China, though limited quantities of isotopes may be produced in other countries for research purposes.

Domestic Production of Key Stable Isotopes: The U.S. is heavily dependent on foreign suppliers of stable isotopes, though by addressing the recommendations of the 2009 Isotope Long Range Plan Report the IDPRA has begun to address domestic vulnerabilities. The potential shortage of ^{7}Li, a critical material needed by the 65 pressurized water reactors producing electricity in the country (as an additive to boron in the cooling circuit), has been identified by the DOE Isotope Program and a GAO study as particularly worrisome. The U.S. nuclear power program uses 500 kg of ^{7}Li annually, with the principal supplier being Russia. The Isotope Program has formed an internal federal working group to mitigate a potential ^{7}Li shortage, and is establishing an emergency reserve.

Recognizing the need for U.S. production of enriched stable isotopes after the calutrons were shut down over ten years ago, the DOE Isotope Program is establishing a new electromagnetic isotope separator (EMIS) facility at Oak Ridge National Laboratory to produce stable isotopes in great demand in the United States. The ORNL 10 mA EMIS was commissioned in 2011; since the end of 2013 the Isotope Program has been supporting the development of a 100 mA ion source to augment production capabilities. In addition, ORNL is being supported to develop EMIS – Gas centrifuge hybrid concepts for isotope separation that should result in significant new production capacity.

The Isotope Program NIDC is responsible for managing and distributing the Nation's inventory of stable isotopes, located at ORNL including ^{48}Ca, ^{69}Ga, ^{87}Rb, ^{37}Cl, ^{195}Pt, ^{146}Nd, ^{146}Sm, ^{99}Ru and ^{66}Zr.

US domestic production of stable isotopes in private industry is essentially limited to Cambridge Isotope Labs (CIL) production of ^{18}O and ^{13}C in Xenia, OH. ^{18}O water is the target material for the production of ^{18}Fl in cyclotrons, used in the drug FDG for PET scans. CIL is a world leader of ^{18}O production, with additional suppliers to the U.S. market including Taiyo-Nippon Sanso (Japan) and Rotem (Israel), Huayi Isotopes (China). The U.S. and World requirements for ^{18}O are more than adequately supplied, at this time.

Other emerging U.S. domestic sources of stable isotopes include use of new technologies, such as Magnetically Activated & Guided Isotope Separation (MAGIS) technology, developed at the University of Texas, Austin. Using low powered lasers and magnetic separators, MAGIS promises low cost and "environmentally friendly" production of stable isotopes, particularly ^{7}Li, for U.S. nuclear power programs. The use of Laser Isotope Separation (LIS), led by GE-Hitachi in Wilmington, DE and Plasma Centrifuge technologies, also show great promise in jumpstarting domestic U.S. production in the years ahead. However, for now, U.S. domestic consumption remains heavily dependent on overseas producers.

New isotope production capabilities typically require significant capital funds and construction time. Such investment has risk. For example, if a promising new medical application fails to perform as expected in later stage trials, the demand for a particular isotope may collapse. On the other hand, if it is successful, the demand may increase by large factors, again creating a shortage in supply until successful commercialization can be achieved. Once a reliable commercial supply is available, DOE must leave the market. On the other hand, if a major customer pulls out of the market, the cost for all other users can increase dramatically.

The challenges for the program are illustrated in Sidebar 11, which presents the history of the production of ^{82}Sr, a key isotope for clinical positron emission tomography (PET) Initially production of ^{82}Sr was made via spallation at the two U.S. production sites (BNL and LANL) and TRIUMF, but soon switched to ^{85}Rb(p,4n). For a period ('90-'95) supply exceeded demand for generators, as there were only a few users. During this period the emphasis was on reliability – getting the active pharmaceutical ingredient (API) and the generators on a regular and reliable basis to the modest number of clinical researchers already using them rather than increasing the user base. The addition of INR (Russia) and iThemba (South Africa) as suppliers was initially done to address reliability issues, but once they came on line they also increased supply. Availability and stability of ^{82}Sr production led to increased demand. As demand for generators increased, supply could keep up and the supply/demand were matched.

The advent of IPF (a dedicated 100 MeV beam line for isotope production at LANL) in 2004 led to increased supply, which was greater than demand for a while, but led to the supply being well-positioned for the steep increase in demand during the '05-'10 period. The increased demand was prompted by a better reimbursement environment (resulting from more users providing better data), better PET instruments, the ^{99}Mo supply shortage and the increasing maturity of the procedure and acknowledgement of the benefits associated with the diagnostic studies.

Up to this time, the percentage of patient potential (GREEN – Right Hand axis in Figure 11 in the sidebar), which corresponds roughly those now getting SPECT Myocardial Perfusion Index with pharmacologic stress and which is growing in absolute terms as the population ages, was a small fraction of the total potential. In the last ~5 years (2009-2014) the absolute patient numbers have increased and the procedure has moved from 'cutting edge research' to 'routine'.

A lack of reliability has become unacceptable at the same time as the need for even larger supplies of ^{82}Sr has increased. The occurrence of extended scheduled beam-off periods of the major facilities produces periodic shortages and overabundances of ^{82}Sr each year that necessitate very intricate and careful management of generator supply in the presence of a constant, and increasing, patient demand. A new accelerator in France, Arronax, provided an additional ^{82}Sr source in this period, but the increasing ^{82}Sr supply has had little effect on the periodic shortages. To add to the challenge, Bracco temporarily withdrew from the market during this period to resolve generator problems; this caused a tremendous stress on the Isotope Program, as revenues were unexpectedly and significantly lost, which forced the Program to expend program funds to maintain expertise and capabilities.

The overall environment has, for some time, been one where supply is increasing only incrementally and restricting growth. This has prompted independent entities to pursue new 'commercial' cyclotrons, the first of which is projected to begin producing ^{82}Sr in 2016. These

Sidebar 11: ^{82}Sr: A Case History for International Cooperation. Status Update – 2014

^{82}Sr supply and demand is shown in Figure 11 below. The amount available at calibration (in arbitrary units) is shown in RED, and generator demand is shown in BLUE (in the same arbitrary units). The individual ^{82}Sr sources are the open arrows and the overall phases are the closed arrows.

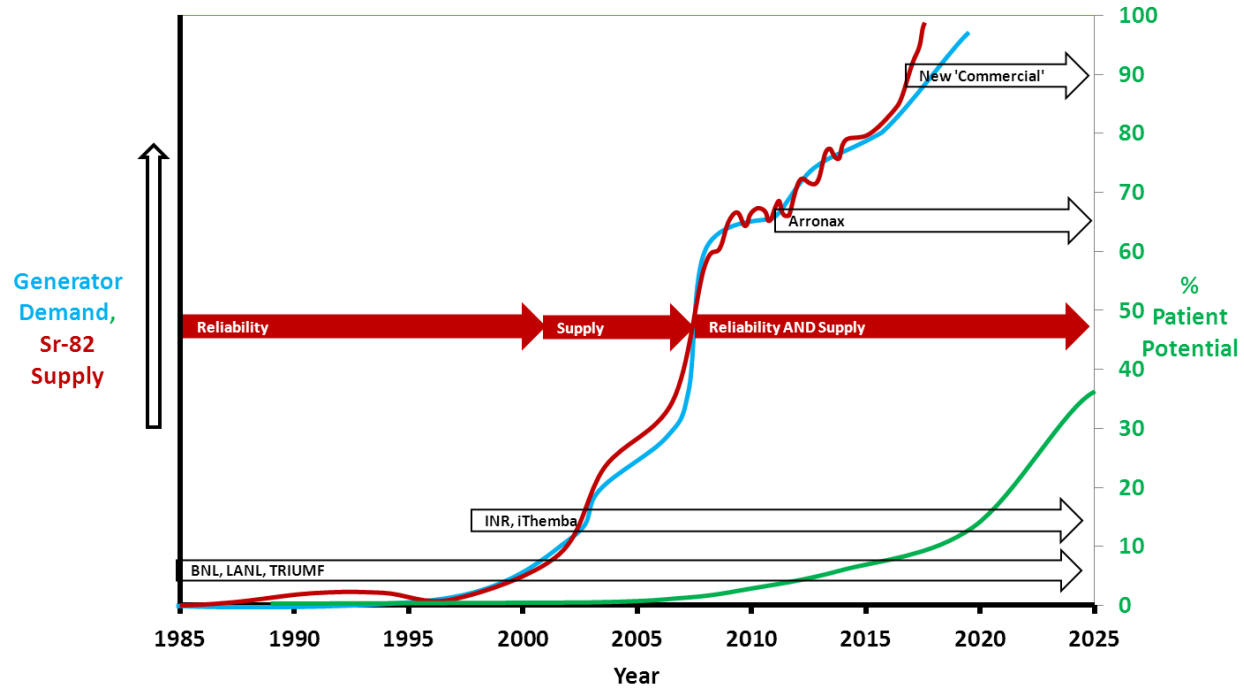

Figure 11: Supply and Demand for ^{82}Sr *(graph courtesy A. Nunn, Bracco)*

Initially production was via spallation but soon switched to ^{85}Rb(p,4n). For a period (’90-’95) supply exceeded demand as there were only a few users of the generators. During this period the emphasis was on reliability – getting the active pharmaceutical ingredient (API) and the generators to the relatively small number of existing clinical research users on a regular and reliable basis, rather than increasing the user base.

The addition of INR (Russia) and iThemba (South Africa) as suppliers was initially to address reliability issues but once on line they also increased supply. As demand for generators increased supply could keep up and the two were matched.

The advent of IPF (LANL) led to increased supply which was greater than demand for a while. This led to supply being well-positioned for the steep increase in demand in 2005-2010 which was prompted by a better reimbursement environment (itself a result of more users leading to better data), better PET instruments, the ^{99}Mo supply shortage and the increasing maturity of the procedure and acknowledgement of the benefits associated with the diagnostic studies.

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Sidebar 11 (cont.)

patient numbers have increased and the procedure has moved from 'cutting edge/research' to 'routine' clinical practice. A lack of reliability has become unacceptable at the same time as the need for supplies of ^{82}Sr has increased. The occurrence of extended scheduled beam-off periods of the major facilities produces periodic shortages and overabundances of ^{82}Sr each year which necessitate very intricate and careful management of generator supply in the presence of a constant, and increasing, patient demand. Bracco temporarily withdrew from the market during this period to resolve generator problems. The advent of Arronax as an additional ^{82}Sr source also occurred in this period but the increasing ^{82}Sr supply has had little effect on the periodic shortages.

The overall supply of ^{82}Sr has, for some time, been increasing only incrementally and thus it is restricting growth. This has prompted independent entities to build new 'commercial' cyclotrons, the first of which is anticipated to begin producing ^{82}Sr in 2016. These should not only increase overall supply but also smooth out the periodic gaps in the existing supply. In this period demand is expected to increase as a result of increases in the total potential patient pool and the routine introduction of absolute tissue flow measurements into the procedure (which are inaccessible to other modalities.) Maintaining the overall reliability of supply during the integration of the new suppliers will be essential to protect the patient population served.

According to Bracco, "only at the point where the reliability of the new API producers has been proven beyond doubt and their integration into the existing generator supply has been successfully demonstrated over an extended period of time would it be appropriate for DOE to consider reducing their involvement."

should not only increase overall supply but also smooth out the periodic gaps in the existing supply. In this period, demand is expected to increase as a result of increases in the total potential patient pool and the routine introduction of absolute tissue flow measurements into the procedure (which are inaccessible to other modalities.) Maintaining the overall reliability of supply during the integration of the new suppliers will be essential to protect the patient population served. Only at the point where the reliability of the new active pharmaceutical ingredient has been proven beyond doubt and its integration into the existing generator supply has been successfully demonstrated over an extended period of time would it be appropriate for DOE to consider reducing their involvement.

This history of ^{82}Sr illustrates the critical role R&D plays in identifying promising isotopes and the central role infrastructure investments serve to increase production and stimulate latent demand. Now that the market for ^{82}Sr had been established, commercial entities are entering. This healthy shift in the market could result in limited demand for ^{82}Sr produced from the Isotope Program. While this is a success story, the sudden loss of the major source of sales could harm the program. To be prepared, the Program must invest in R&D and infrastructure to develop production capacity for promising new isotopes that will meet future demand, lead to new industry, and further technological developments.

Outline of the response to these challenges

In the next five chapters, the issues raised in this chapter will be addressed and recommendations made to tackle remaining concerns. Chapters 6 and 7 outline the capabilities of the four major production techniques and the infrastructure investments needed for an optimal program. Chapter 7 addresses issues in research and development and identifies the critical needs in this area to allow the program to meet future demand. Chapter 8 describes the intellectual capital and skilled workforce needed for success of the program. Chapter 9 addresses needs in program operations. The implications on the budget to achieve an optimal program are presented in Chapter 10.

Chapter 6: Sources of Isotopes for the Nation

There are many different sources of isotopes. These include the use of mass separators on inventories of both stable isotopes and relatively long-lived radioactive isotopes. Both accelerators and reactors can be used to create isotopes through nuclear reactions. Finally, there are opportunities to obtain isotopes that are produced as by-products. In this chapter we discuss each of these sources in turn, identifying challenges and opportunities for their utilization.

6.A: High Purity Stable and Radioactive Isotope Mass-Separation Capability

Chapter 5 of the 2009 NSACI report, *Isotopes for the Nation's Future – A Long Range Plan* [NSACI09] discussed the importance of stable isotope applications, and their production, supply, and availability. This section will update the 2009 information, focusing on progress toward achievement of NSACI's previous recommendations, and will conclude with new recommendations based on contemporary observations.

The 2009 NSACI recommendations are reiterated below for reference:

- Maintain a continuous dialogue with all interested federal agencies and commercial isotope customers to forecast and match realistic isotope demand and achievable production capabilities.
- Support a sustained research program in the base budget to enhance the capabilities of the Isotope Program in the production and supply of isotopes generated from isotope reactors, accelerators, and separators.
- Construct and operate an electromagnetic isotope separator facility for stable and long-lived radioactive isotopes.

Stable Isotope Demand and Supply

As discussed in the 2009 NSACI report, the enrichment of "light" stable isotopes (e.g., ^{13}C, ^{17}O, ^{18}O, ^{10}B, and ^{11}B) has been privatized as commercially viable ventures that deploy affordable separation technologies such as distillation, chemical exchange, or thermal diffusion. The heavier stable isotopes, however, require more sophisticated technologies such as electromagnetic isotope separation (EMIS), gas centrifuge, gaseous diffusion, plasma separation, or laser separation. These are far more complicated processes that are capital intensive and often involve sensitive technology. Most of the existing enrichment capabilities of these types have been developed as outgrowths of major uranium enrichment programs and could not have been economically justified on the basis of stable isotope markets alone. Even the operation of such facilities is not commercially viable and typically relies on government subsidy. In addition, the security requirements associated with the dual-use separation technologies adds to the cost of construction and operation, and significantly complicates deployment of enrichment capabilities by both government entities and the private sector.

The vital need for a dependable domestic source of these heavier enriched stable isotopes was well established in the 2009 NSACI report, and this message has been reinforced in subsequent years. The NIDC recently categorized worldwide demand for the heavier stable isotopes into

two primary market sectors [NIDC13]: The large bulk quantity market; and the small quantity market (< 1 kg/yr).

The large quantity market (estimated at $100M worldwide), which can involve production and distribution of thousands of kilograms per year, is dominated by Russian production (85%) with the remainder produced in the Netherlands (15%) by URENCO. The most important isotopes in this category are ^{203}Tl, ^{191}Ir, ^{88}Sr, and ^{68}Zn used as medical radioisotope precursors, Zn (depleted in ^{64}Zn) for corrosion prevention, ^{74}Se as a precursor to ^{75}Se used in gamma radiography, and ^{76}Ge and ^{28}Si used in nuclear physics applications. Gas centrifuge separation is the primary technology used in this market segment.

The small quantity market is comprised of a large number of orders annually (200-300) for small research quantities, and is supplied by DOE Isotope Program legacy inventories at ORNL, and from Russia. The majority of isotopes in this sector were enriched by the electromagnetic separation process using equipment dating back to the 1940s and 1950s. The annual revenue for the DOE Isotope Program from sales of stable isotopes from the U.S. legacy inventory averages approximately $670K. This average annual DOE sales figure does not include stable isotopes that were transferred internally within the program for the production of radioisotopes, and reflects a discount for researchers. In 2009, NSACI reported that the U.S. legacy inventory has been declining since calutron operations were shut down in 1998. Table 9 provides an update on the estimated remaining inventory of select stable isotopes at Oak Ridge, based on sales and inventory information from 2008-2012, and also highlights the stable isotopes purchased since the 2009 report.

Via the NIDC and through forums such as the annual federal workshop on isotope supply and demand, the Isotope Program stays well informed on the isotope needs of federal agencies and other isotope users so that the demand from both market sectors can be characterized. Table 18 (in Appendix 8) provides a table of stable isotope demand developed by NIDC in 2011 (details of the quantities demanded have been omitted as business sensitive information). The table establishes a high priority for important medical precursor isotopes such as ^{203}Tl, ^{88}Sr, etc. Although this market is currently being supplied by foreign sources, the Isotope Program believes that it is important for the U.S. to be in a position to re-establish production in this key area in order to eliminate vulnerabilities. Current developments are also under way to establish U.S. reactor and accelerator capabilities to produce ^{99}Mo/^{99m}Tc using alternate technologies. This will increase the domestic demand (and the associated production priority for the isotopes listed in Table 18 in Appendix 8) for the enriched precursors ^{98}Mo and ^{100}Mo that are currently only available from foreign sources.

The Isotope Program also gives priority to those precursor isotopes that have important national security applications, such as ^{62}Ni, the precursor to ^{63}Ni which is the active component in contraband and explosive detection devices at airports. ^{74}Se is a precursor to ^{75}Se which has important nondestructive testing (NDT) applications in ship building and oil & gas pipelines. ^{87}Rb is an important component in communications equipment used by the private sector in cell phone signal transmission and for satellite communication devices important for national defense.

Table 9: Inventory Projections for Select Stable Isotopes in Short Supply in the Remaining Oak Ridge Inventory [FE12] and Stable Isotope Purchases Made since 2009

Stable Isotope in Oak Ridge Inventory	Remaining Years of Inventory Based on Average 5-yr Sales	Isotope Purchased	Quantity Purchased (g)
$^{157}Gd_s$	0	^{136}Ba	12.5
$^{204}Pb_s$	0	^{69}Ga	20.0
$^{207}Pb_s$	0	^{157}Gd	10.0
^{96}Ru	0	^{202}Hg	3.3
$^{150}Sm_s$	0	^{176}Lu	1.5
^{181}Ta	0	^{100}Mo	16.7
^{51}V	0	^{150}Nd	4.9
$^{180}W_s$	0	^{186}W	70.0
^{157}Gd	0.5	^{62}Ni	23.8
^{35}Cl	6.6	^{62}Ni	16.3
^{40}K*	12.5	^{62}Ni	50.0
^{99}Ru	14.5	^{62}Ni	50.0
^{46}Ca	15.6		
^{195}Pt	16.3		
^{69}Ga	17.9		
^{203}Tl	18.9		
^{198}Pt	25.6		
^{62}Ni	12.5		

$_s$ = second pass enrichment, exceeding 99%

*Historically tracked as part of the stable inventory

There are also emerging priorities associated with unique applications involving large quantities of specific enriched stable isotopes that are needed to conduct key research. For example, approximately 30 kilograms of enriched ^{76}Ge is being incorporated into a nuclear physics research experiment called the Majorana Demonstrator Project. The Majorana collaboration will investigate the nature of the neutrino, the neutrino mass spectrum, and the absolute mass scale [MA11]. ^{76}Ge is currently available only from a foreign source, and potential future needs for^{76}Ge in support of a one-tonne version of the Majorana experiment, if approved for funding, are projected to total approximately 1,000-1,500 kg. Foreign sourcing of this material, representing a very substantial expenditure, may be unacceptable from a geopolitical standpoint.

Other examples include: The Cryogenic Underground Observatory for Rare Events (CUORE), an Italian-Spanish-US nuclear physics experiment installing TeO_2 crystals containing 200 kilograms of ^{130}Te; and The Avogadro Project, which involves development of a worldwide weight standard based on pure ^{28}Si crystal balls, and requires kilogram quantities of this isotope.

The dangers of reliance on foreign sources (e.g., quality control and reliability) for the supply of these and other stable isotopes for important medical applications, industrial productivity, basic research, and national security were outlined in the 2009 NSACI report. However, since then it has been reported that Russia may reduce their electromagnetic separation operations, and that the governmental owners of URENCO (Germany, Great Britain, and the Netherlands) are in the process of divestiture. It remains unclear what will happen to stable isotope production in the Netherlands if URENCO, the primary mission of which is uranium enrichment, is sold to commercial interests.

DOE's Progress Toward Re-Establishment of a Domestic Supply

Substantial and encouraging progress has been made by the DOE Isotope Program toward mitigating this risk of foreign dependency for stable isotope production. In 2009 the IDPRA Program began investing in research and development toward the modernization of electromagnetic isotope separation (EMIS), since resurrection of the Oak Ridge calutrons was considered infeasible. IDPRA also funded a study to examine the feasibility and advantages of pairing gas centrifuge isotope separation (GCIS), a high throughput low enrichment technique, with EMIS, a low throughput, high enrichment technique. Outside of the IDPRA program Idaho National Laboratory (INL) operates a small-scale mass separator for programmatic purposes (Sidebar 12) and is preparing to operate a second research-scale separator designed for use with radioactive isotopes.

Development of the pilot capability at ORNL began with the design, assembly, and demonstration of a 10 mA (nominal current) EMIS prototype. The prototype, pictured in Figure 12, used a Freeman ion source, which is commonly used in the semiconductor industry. IDPRA then supported the examination of alternative ion source concepts for potential multi-program applications; this work was leveraged by an ORNL Weinberg Fellowship. This resulted in the development of a prototype non-ambipolar electron driven ion source (NEDIS) as a means of compensating for the inherent weaknesses in the Freeman ion source (such as its short operational life expectancy). Having successfully proven the concept, IDPRA is now funding an upgrade project to re-fit the 10 mA prototype EMIS with the NEDIS in order to achieve ion currents that approximate the former calutron capability.

IDPRA has also funded a pilot production development effort that will integrate the upgraded EMIS with a small gas centrifuge cascade to achieve the pilot production philosophy. The integrated system is being developed in re-purposed ORNL laboratory space, which the IDPRA Program modified to host the necessary infrastructure for safe and secure GCIS and EMIS operations. Under the IDPRA-funded Enriched Stable Isotope Production Pilot (ESIPP) project, the integrated system will be automated to minimize operational costs. ORNL anticipates initiating pilot scale operations, with a single calutron-equivalent EMIS paired with a 9-unit GCIS cascade, during FY17.

Sidebar 12: Small-Scale Isotope Separation at Idaho National Laboratory Developed by the Nuclear Forensics Community

Since 2009 researchers from Idaho National Laboratory (INL) have been operating a mass separator for stable isotope separations [CA13] with support from the Federal Bureau of Investigation. The instrument operates outside the scope of the DOE Isotope Program for programmatic purposes, although there has been collaboration involving the exchange of technical instrumentation. The instrument was originally developed in the 1970's (Figure 11) for separating isotopes of short-lived fission products from the spontaneous fission of ^{252}Cf [CA79]. The system has also supported the separation and isolation of gaseous fission product isotopes.

Recent ^{134}Ba production runs have emphasized increasing isotopic purity (isotopic abundances typically exceed 99%). The throughput of this instrument is dependent upon the element being separated; for ^{134}Ba the throughput is approximately 5 micrograms per hour starting with a natural abundance Ba metal target. Run times on the order of 40 to 50 hours have been obtained routinely. In addition to Ba, separated isotopes of Sr have been produced for research applications. Other elements with isotopes of interest for separation/enrichment include: Ba, Zr, and Ni and rare earth elements.

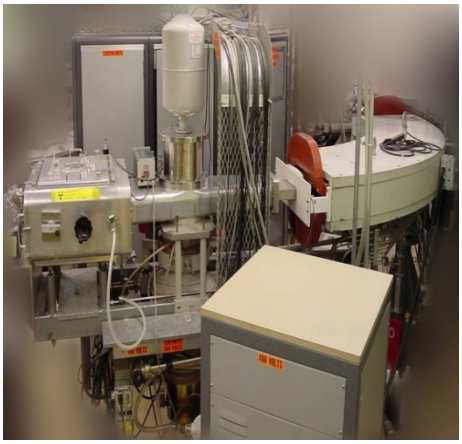

Figure 12: INL stable mass separator

This instrument is assisting maintaining the US isotope community's technical expertise in electromagnetic separation and ion source design. Several early-career staff members and PhD students have been trained in EMIS techniques. A second, research-scale mass separator designed for use with radioactive isotopes is undergoing commissioning at INL.

Figure 13: The EMIS 10 mA prototype inside of the upgraded host facility (Dec 2014)

The pilot capability planned for completion in FY17 is a major step in the right direction, and will produce research quantities of enriched isotopes. However, it does not yet provide for the large-scale production of stable isotopes discussed in the 2009 NSACI report. In that report, the Subcommittee envisioned a raw feedstock throughput of 300-600 mA, which would require the equivalent of four upgraded EMIS units like the one currently under development. Pending evaluation of the pilot unit, the Isotope Program plans to expand the capabilities at ORNL to meet this goal. The need for a greater production capacity is evident in Figure 13, which shows that approximately four EMIS units would be needed to meet annual demand for the top 10 selling isotopes averaged over the period 1997-2011, if those four units were operational 70% of the time, 24 hours per day, and seven days per week. The figure also shows which of the top ten isotopes during this period would be candidates for pre-enrichment using GCIS, which would reduce the number of EMIS hours needed to meet enrichment demands.

As can been seen in Figure 12, the host facility has sufficient floor space and infrastructure capacity for future expansion. Conceptual floor plans exist for as many as three upgraded EMIS units accompanied by a less-than-50-unit GCIS cascade, or two EMIS units with less than 100 GCIS units. Such an expansion would likely be sufficient to meet historical demands for many research isotopes, depending on the individual isotope of interest. The ESIPP was intentionally designed to be completely scalable and located in a facility that could be easily expanded. Should production feasibility be successfully demonstrated in FY 2017, the Isotope Program intends to pursue upgrades in capability and has been engaging federal agencies in this regard for the past year. NSACI encourages the IDPRA Program to establish a financial strategy to ensure that long-term funding will be available to reliably meet annual research production needs, and to investigate a path that would enable expanded production to meet a critical demand scenario involving the failure of a crucial foreign supply.

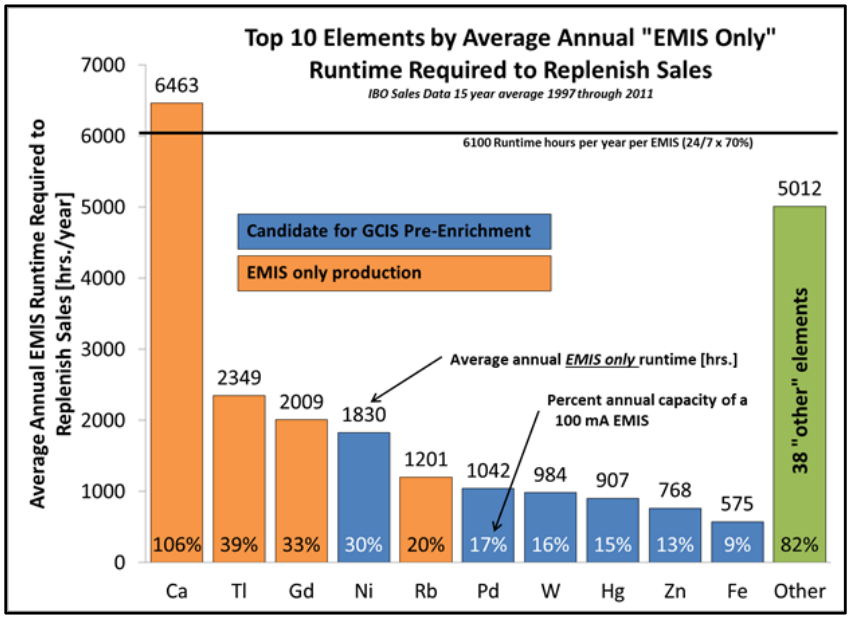

Figure 14: Top 10 Elements by Average Annual EMIS-Only Runtime

A large array of chemical and material support functions are required to provide enriched stable isotopes in the physical forms required by various research and application user communities. These post-enrichment capabilities are essential to enabling research and applications since the output of enrichment devices is typically not in a directly usable form. Traditionally, isotopes enriched on the calutrons were extracted and stored in their most stable forms, typically oxides or nitrides. At ORNL, these storage forms are chemically and physically converted as needed to user-requested forms, which may include high-quality metal foil and wire, thin films, sintered pellets, and chloride salts.

The ORNL Isotope Program maintains an array of expertise in handling small (milligram to gram) quantities of this highly valuable material. But even with experienced staff the traditional conversion processes often result in a significant loss of the valuable enriched materials and add significant cost to the end-user. Often the end-user only requires a few milligrams of a converted isotope, but experience with the conversion process has resulted in the establishment of minimum batch quantities to reduce material losses that are higher than end-user demands. Since it is unfair for individual researchers in need of very small quantities to bear the entire cost of minimum batch processing that exceeds their demand, excess conversion cost is sometimes absorbed by the Isotope Program.

The research and development of optimized chemical and materials processing techniques to achieve high efficiency conversion of small quantities of material represents an opportunity for the program to reduce the overall cost of doing research with enriched stable isotopes. The proper utilization of new enrichment capabilities will require direct collaboration of Isotope Program staff with external researchers, and this presents an opportunity to develop optimized processing techniques tailored to their individual needs. For example, the EMIS can provide a chemically and isotopically pure beam of nearly any isotope. This beam could be implanted on an end-user's substrate and used directly, thus eliminating the cost and losses associated with post-processing, substantially reducing the total cost of isotopes, and allowing for new research opportunities.

Following the recent successes in the development of modern EMIS for stable isotope production that have been outlined in this chapter, the community is now equipped to apply this technology to the construction of a production scale EMIS for radioisotopes. To provide such a capability domestically would significantly enhance existing and future research in the physical sciences, the medical programs, and national security.

Recommendations

- **We recommend completion and the establishment of effective, full intensity operations of the stable isotope separation capability at ORNL**

  The subcommittee is pleased with the progress that has been made since the 2009 NSACI recommendation toward the establishment of a stable isotope separation capability. Without this effort the U.S. is dependent on foreign sources for materials critical to the health and safety of the nation. This ongoing effort should continue until the separation capability is fully established, the intensity goal of throughput comparable to a calutron (~100 mA ion current) has been achieved, and the separator is available for routine use. To achieve the goal

for separator throughput, the Isotope Program is investing in the development of new ion source technology.

This facility will provide a reliable U.S. source of high-purity stable isotopes, many of which are currently available only from Russia, and will require, among other things, the allocation of a base operations budget for the separator.

As part of the preparation for this capability it is important to plan for a smooth transition to sustainable, domestic, stable isotope enrichment operations by developing a production campaign strategy aimed at meeting a documented and prioritized demand. It is also necessary to develop an associated expansion strategy to build on the emerging pilot capability at ORNL and eventually realize NSACI's vision for a domestic supply, including both historic demand for research quantities of stable isotopes, and the ability to respond to a supply crisis resulting from an interruption in the foreign supply of high priority bulk quantity stable isotopes. Finally, it is essential to establish a funding strategy that recognizes the intrinsic value of a domestic source of enriched stable isotopes, including adequate base funding to secure the capability into the foreseeable future.

R&D into advancing engineering services capabilities which offer the potential to minimize the loss of high-value enriched materials during post-enrichment processing are also to be encouraged. This latter effort should be done in close collaboration with end users.

Finally, NSACI reiterates its 2009 recommendation to develop a separator for research quantities of radioactive isotopes.

- **We recommend an increase in the annual appropriated budget to realize the opportunities associated with high-impact infrastructure investments and to maintain a stable funding base for reliably operating and continually improving facilities. Specific opportunities for the period covered by this Long Range Plan include:**

  - ***Develop a strategy for the re-establishment of a separator for radioactive isotopes to support research*** – The isotope community has expressed the need for high specific activity, mass separated radioactive isotopes. A strategy for establishing a domestic capability for high purity radioactive isotopes should be developed. This capability is important to physical science programs, the medical community, and our national security. While chemical techniques can be used to separate the desired radioisotope from other elements, the selectivity to gain the isotopic purity desired by the community cannot be achieved without the development of electromagnetic separators for radioactive materials.

6.B: Accelerator-Based Isotope Capabilities

Accelerator isotopes are typically neutron deficient and are produced in either cyclotrons or linear accelerators by proton, deuteron, alpha, or heavy particle bombardment. Accelerator isotope applications generally complement reactor isotope applications, and accelerator isotopes

usually decay by β, γ or positron emission or electron capture. Accelerator beam parameters, especially beam energy and integrated beam current (current x time), are important considerations in the production of isotopes. Beam energy determines what isotopes are produced (and by what nuclear reaction) and integrated beam current determines how much is produced. Low energy cyclotrons (<30 MeV) are generally used to produce short-lived isotopes (^{11}C, ^{15}N, and ^{18}F) that are used in clinical positron emission tomography (PET) and PET R&D. However, many other isotopes can be made at lower energies as discussed below. Several commercial isotopes are produced in 30 MeV cyclotrons operated by industrial isotope producers and radiopharmaceutical manufacturers, e.g. ^{111}In, ^{201}Tl, ^{67}Ga and ^{123}I. Higher energy accelerators are usually operated by government laboratories and make products that require higher energy, such as ^{82}Sr [IAEA10]. This discussion does not duplicate the information in the 2009 NSACI report [NSACI09A], but provides updates on most sections to make the reader cognizant of the current situation for accelerator isotope production.

Scope of Accelerator Based Capability Updated

Commercial Cyclotrons Update: Low energy accelerators have been used by radiopharmaceutical manufacturers for many years [IAEA08]. These accelerators typically operate at 30 MeV with beam current usually up to 1 mA. These are more than adequate to supply the radioisotopes ^{201}Tl, ^{111}In, and ^{123}I, as well as other isotope for radiopharmaceutical applications and clinical nuclear medicine. Recently, one supplier has devoted beam time from their cyclotrons for the production and distribution of ^{68}Ge. This is the first radionuclide introduced into commercial distribution from these industrial cyclotrons in many years. The radiopharmaceutical companies producing their own radioisotopes include Mallinckrodt, GE Healthcare, Lantheus, and Nordion. The radiopharmaceutical manufacturers do this to ensure the reliable availability of radiopharmaceuticals for the clinical practice of nuclear medicine. Most of these commercial producers have multiple cyclotrons for production, but since the cyclotrons are in various stages of life cycle, future capital investments for each manufacturer will be different. There are more than a dozen commercial cyclotrons operating in the U.S.

University Cyclotron Update: The DOE Isotope Program has initiated developing a network of university cyclotrons to assist in production of isotopes that are in short supply, can be more readily produced at those facilities, or take advantage of unique capabilities of a particular university facility. Comments on the production capabilities of university cyclotrons follow.

A large number of small, more affordable, PET cyclotrons have been installed in Universities over the last couple of decades. These cyclotrons generally have low energy proton beams (10 – 19 MeV) that are primarily used to produce PET isotopes (e.g. ^{11}C, ^{18}F, ^{13}N, ^{15}O) for in-hospital use. Regional commercial radiopharmacies have taken over production of the ^{18}F supply for some hospitals having cyclotron facilities, resulting in increased beam availability at those University PET cyclotron facilities. While not all centers have the infrastructure for utilizing irradiated solid targets, those cyclotrons that do are capable of producing significant amounts of radioisotopes. Washington University and the University of Wisconsin, Madison are two notable examples, as they routinely produce a number of radioisotopes and ship them to customers. Several of isotopes that they produce (e.g. ^{64}Cu, ^{44}Sc, ^{86}Y, ^{76}Br, ^{77}Br, ^{72}As) are listed in Table 12 below as important isotopes for future needs in theranostic isotope pairs useful in personalized

medicine [QA04]. These universities are providing a valuable service in meeting some of the U.S. isotope needs. The DOE Isotope Program has helped both of these university sites by providing equipment that allows them to produce higher quantities of isotopes in short supply. DOE has begun to enter into discussions on how these universities can participate in a University Isotope Production Network. This concept has merit, and should be pursued further. Irrespective of the mechanism by which these universities participate in the DOE network, DOE's contribution to their production should be noted on their web sites and in published materials. In particular, the infrastructure put in place at several of these sites has allowed for the widespread use of ^{64}Cu and ^{89}Zr and initiation of clinical trials.

Some universities have larger cyclotrons with higher beam energies (up to 50 MeV) and different types of particle beams that could potentially be used to produce isotopes in short supply. DOE has considered four university cyclotron sites with larger cyclotrons as potential sites to join the DOE Isotope Production University Network. Those sites are: University of Washington, Duke University, Texas A&M and University of California at Davis. While these university sites are not routinely producing radioisotopes for distribution, they have cyclotrons with capabilities of producing radioisotopes in short supply. Although the cyclotron sites have the capability to produce other radioisotopes, the immediate need is for production of the high priority isotope ^{211}At. It is important to note that with a short half-life ($t_{1/2}$ = 7.2 h), ^{211}At should be produced in regional cyclotron centers, as the amount received by customer could be as low as 10% of that shipped if it has to be in transit overnight. Production of ^{211}At requires an alpha-particle beam that these university cyclotrons have. The University of Washington has become the first university site to participate in the DOE network. ^{211}At is routinely produced on the UW Medical Cyclotron for preclinical studies, and, in the near future, clinical studies. Over the past 5 years DOE has provided funding through research grants to improve the process of isolating the ^{211}At from bismuth targets and plans to provide some base funding to assist in the production efforts. Other such University arrangements are being considered.

DOE Higher Energy Accelerators Update: DOE continues to use the same suite of facilities that were described in the 2009 NSACI report for the production and distribution of neutron-deficient radioisotopes. They continue to use international accelerator facilities to complement the in-house capabilities. DOE has made significant capital investments on their "in-house" capabilities since 2009 and these are described below, as well as updates concerning the international facilities. Characteristics of these accelerator facilities are given in Table 10.

Brookhaven National Laboratory Specific Capability Improvements: Brookhaven has received significant capital investment funds for both the Target Processing Laboratory (TPL) and the Brookhaven Linac Isotope Producer (BLIP) as listed below.

Target Processing Laboratory Projects

- Automate radioisotope dispensing
- Reorganizing the TPL to optimize work flow

BLIP Facility Projects

- Raster Project
- Linac Intensity Upgrade

These investments will be approximately $6.2 M when completed in the fall of 2016.

Los Alamos National Laboratory Specific Capability Improvements: Los Alamos has seen capital improvements in both the hot cell facilities and the Isotope Production Facility (IPF) as listed below.

Hot Cell Facility Projects

- TA-48 Hot Cell 13 Electrical System Upgrade
- TA-48 Hot Cell Window Refurbishment
- TA-48 Hot Cell Manipulator Replacement
- TA-48 Hot Cell Train System Upgrade
- TA-48 Hot Cell HVAC - Replacement
- TA-48 Hot Cell 3&4 Electrical System Upgrade

Isotope Production Facility Projects

- IPF Beam Window Replacement
- IPF Target Control System Upgrade
- IPF Germanium (Ge) Detector Installation
- IPF Personnel Contamination Monitor (PCM)
- IPF Chain Drive

These investments totaled approximately $4.5 M plus installation costs for the new IPF chain drive that is still in progress.

International Accelerator Facilities: In addition to DOE's Laboratory facilities, the DOE Isotope Program coordinates the production and output from international accelerator facilities that in the past has been described as a *Virtual Isotope Center*. This concept involves collaborations dating back to the early 1990's with TRIUMF in Vancouver, British Columbia, Canada followed closely by collaborations with the Institute of Nuclear Research in Troitsk, Russia. It has also included the iThemba Laboratories in Faurve, South Africa and the Paul Scherrer Institute in Villigen, Switzerland. Originally, the collaborations were directed at ^{82}Sr, ^{68}Ge, ^{103}Pd, and ^{67}Cu, but recently have focused exclusively on ^{82}Sr (See Sidebar 11 in Chapter 5 above). Recently the Arronax Facility in Nantes, France has been added to DOE's list of collaborators. In most all of these collaborations, the international facilities irradiate targets for production of DOE distributed isotope products, and they ship these irradiated targets to either Los Alamos or Brookhaven for chemical processing, purification, dispensing and distribution to DOE customers. Details of these higher-energy accelerators are given in Table 10 below.

The Arronax facility is the newest-high energy accelerator globally to be commissioned and utilized for isotope production. The multi-particle capability for the accelerator (see Table 11) makes it a more versatile isotope producer compared to the other facilities listed in Table 10, and makes it an interesting possibility for isotope production R&D, and ultimately for production of research isotopes of interest to various research constituencies. Further collaborations between Arronax and the DOE Isotope Program are encouraged to take advantage of this flexible accelerator for research isotope availability.

Table 10: Parameters of Government-Operated Higher-Energy Accelerator Facility Beams

Facility	Energy MeV	Beam current (μA)	Availability Months/yr.	Main Isotopes Supplied
IPF	100	250	6 - 8	^{82}Sr, ^{68}Ge, ^{22}Na, ^{67}Cu, ^{32}Si, ^{73}As, ^{109}Cd, ^{72}Se, ^{88}Y
BNL	200	105	4 - 6	^{82}Sr, ^{68}Ge, ^{7}Be, ^{67}Cu, ^{86}Y, ^{65}Zn, ^{52}Fe, ^{83}Rb
INR	160	100	3 - 6	^{82}Sr, ^{68}Ge, ^{22}Na, ^{103}Pd, ^{109}Cd
iThemba	66	120	6 - 8	^{82}Sr, ^{22}Na, ^{68}Ge, ^{73}As
TRIUMF	500 100	150 100	6 - 8	^{32}Si, ^{82}Sr
PSI	72	10 - 70	as required	^{82}Sr, ^{68}Ge, ^{67}Cu
Arronax	70		as required	^{82}Sr, ^{64}Cu, ^{211}At

Table 11: Multi-Particle Capabilities of the Arronax Facility

Extracted Particles	Energy Range (MeV)	Highest Possible Current (μAe)	Most Common Current Range (μAe)
H+	35 - 70	375 x 2	0.05 – 100 x 2
He2+	70	70	0.07 – 0.1
HH+	35	50	0.1 – 1
D+	15 - 35	50	0.05 – 1.2

Current Status and Impacts of the Production Capability

The current state of the production capacity is captured in the bullets below. They describe the major products produced in each type of accelerator, and provide the impact that each production capability has on isotope availability.

- Commercial cyclotrons: Currently produce ^{201}Th, ^{111}In, ^{123}I, and other commercial isotope products. Since 2009 one supplier has developed ^{68}Ge production capability at 30 MeV. They are distributing this product commercially to radioactive source manufacturers and to some researchers. These cyclotrons satisfy customer requirements for commercial accelerator isotopes, but have little impact on research isotope availability.

- University PET cyclotrons: Currently produce ^{18}F, ^{11}C, ^{15}O for PET imaging. Since 2009 several of these cyclotron facilities have developed capabilities for production of longer-lived radioisotopes as described above. These activities have been facilitated in some cases by DOE investment. Currently most are still underutilized with respect to beam availability. These cyclotrons satisfy needs of clinical PET centers and radioisotope research programs at each University, and are having an increasing effect on other research isotope availability. They could have much larger impact if efforts for coordinated production from these facilities could be realized as discussed above and in the recommendations.
- DOE high-energy accelerators: Currently produce ^{82}Sr, ^{68}Ge, ^{22}Na, ^{73}As, and are capable of enhanced research isotope production. Each facility has extensive hot cell facilities to support isotope production. Since 2009 DOE has funded specific core R&D activities at these facilities to increase impact on research isotope availability. Examples include support for ^{67}Cu availability, and R&D into the ^{225}Ac production. As additional resources are available these facilities could make much larger impacts on research isotope availability.
- International high-energy accelerators: Currently produce isotopes independently and in collaboration with the DOE. Processing capabilities are variable from accelerator to accelerator. These collaborators help to satisfy customer requirements for "niche" commercial accelerator isotopes, and have local impacts on research isotope availability. These accelerators could also have a greater impact with additional resources.

Current Deficiencies in the Production Capability

In the 2009 NSACI report the major deficiency in the current accelerator isotope production capability was identified as the lack of capability for the production of accelerator isotopes for research and development requirements of multiple research constituencies. Clearly DOE has made major strides in addressing this deficiency. They have established core research programs at the national laboratories that are addressing technology needs for research radioisotopes. They are also supporting R&D at university cyclotrons with a similar goal. Both of these initiatives are bearing fruit and will continue to be productive in the future as resources are available. They are making significant progress in developing flexibility and reliability of research isotope supply. Clearly DOE needs to continue these efforts. Further, they have taken steps to develop public/private partnerships to further increase the availability of both commercial and research isotope supplies. While these efforts are underway, the hope is that one or more of these initiatives can successfully establish accelerator isotope production at medium energies that will complement the capabilities of industrial and university low-energy cyclotrons, and the higher-energy DOE accelerators. One or more successful public/private partnerships would go a long way toward meeting the flexibility and reliability that is required for research isotope availability. This will, in large part, serve to satisfy the 2009 recommendation to establish a dedicated medium energy cyclotron facility for research and isotope availability. The need for that facility had been driven significantly by isotopes identified by NIH in 2009 as being in short supply; recent requests for isotopes by NIH indicate that this particular urgent need is no longer there. Finally, there is also the possibility that harvesting of isotopes at FRIB could serve some of the need for these isotopes.

There are many targets of opportunity for both national laboratory and university research to address availability of research isotopes. Table 12 lists those radioisotopes that are of interest in

Table 12: Radioisotopes of Interest in Medicine and their Major Production Routes*

Isotope	$T_{1/2}$	Reaction	Comment/Availability
^{44}Sc	3.93 d	^{44}Ca(p,n)	Low Energy Protons
^{47}Sc	3.35 d	^{50}Ti(p,α)	Enriched target needed
^{64}Cu	12.7 h	^{64}Ni(p,n)	University network
^{67}Cu	3.79 d	^{70}Zn(p,α)	Enriched target needed/Spall. Mo
^{67}Ga	3.62 d	^{70}Zn(p,2n)	Commercial
^{68}Ga	1.13 h	^{68}Zn(p,n)	Low Energy Protons/generator
^{68}Ge	271 d	^{68}Ga(p,2n)	Used to make ^{68}Ga via generator
^{72}As	26.0 h	^{72}Ge(p,n)	Low Energy Protons
^{77}As	38.8 h	^{80}Se(p,α)	Low Energy Protons
^{76}Br	16.2 h	^{76}Se(p,n)	Enriched target needed
^{77}Br	57.0 h	^{nat}Mo(p,spall)	High Energy Protons
^{86}Y	14.7 h	^{86}Sr(p,n)	University network
^{90}Y	64.1	^{90}Sr generator	Commercial
^{89}Zr	3.27d	^{89}Y(p,n)	University network
^{99m}Tc	6.0 h	^{99}Mo generator	Commercial
^{111}In	67.2 h	^{112}Cd(p,2n)	Commercial
^{117m}Sn	14.0	^{116}Cd(α,3n)	High energy alphas
^{123}I	13.2	^{124}Xe(p,2n)	Commercial
^{124}I	4.18 d	^{124}Te(p,n)	University network
^{131}I	8.0 d	Fission product	Commercial
^{149}Tb	4.12 h	^{197}Au(p,spall)	Online isotope separator
^{152}Tb	17.5 h	^{197}Au(p,spall)	Online isotope separator
^{161}Tb	6.91 d	^{197}Au(p,spall)	Isotope separator
^{177}Lu	6.65	^{176}Lu + n	Commercial via n capture
		^{180}Hf(p,α)	proton reaction for high Specific Activity
^{195m}Pt	4.0	n capture	
^{198}Au	2.69	n capture	High Specific Activity from ^{198}Pt(p,n)
^{211}At	7.2 h	^{209}Bi(α,2n)	University network
^{211}Rn	14.6 h	U/Th(p,spall)	High Energy/^{211}At Source
^{223}Ra	11.4 d	Decay chain	Commercial
^{225}Ac	10.0 d	Multiple routes	Demand outstrips supply

* Note: with the exception of the isotopes identified as commercial, demand regularly outstrips supply.

medicine, many as theranostic agents [RU89, RU09, QA01]. Those available via the commercial route are included for completeness. There are several available from the university network. However the vast majority are not readily available, not so much because of the difficulty in producing them but the challenges of making sufficient amounts because of the need for enriched targets.

New and Existing Scientific and Technical Challenges

The scientific and technical challenges of accelerator isotope production and applications R&D are myriad and have not changed substantially since 2009. Any new isotope production methodology for a research isotope involves science challenges that include everything from nuclear physics to materials science to chemical separations technology to product quality and quantity to waste identity, handling and disposal. These remain similar to the list in the 2009 report. There are a number of existing technical challenges in accelerator design, target development, and radioactive materials mass separation equipment that need to be addressed to improve the availability of isotopes. Examples include:

- There is a need to conduct R&D on the use of photon (electron) accelerators in isotope production. This alternative route may be useful in producing radioisotopes in short supply from less costly target materials.
- There is a need to develop and build more cost effective accelerators with high beam currents for isotope production, so that the quantity of isotope produced per accelerator is greatly increased. An example is the need to build an alpha particle accelerator with a beam current of hundreds of microamperes so that larger quantities of ^{211}At can be made available on a regional basis.
- With the building of higher current beams, there is a need to investigate new designs, materials and cooling methods for targets used in isotope production. This potentially includes new liquid target designs as well as solid target designs.
- There is also an impending need to design and build a radioactive isotope mass separator. This could be used to produce the high specific activity radioisotopes required in medical applications. It could also be used for production highly purified radioisotopes needed for chemical and physical studies of elements, and the purified isotopes could be used to make traceable materials.
- There are significant opportunities to harvest unused isotopes created as a by-product of research at FRIB. In the process of producing a rare isotope for a primary user, hundreds to thousands of other isotopes are produced in the target and water beam dump. R&D is needed on collection and separation schemes for isotopes collected in water (or other optimized catcher materials) at FRIB to take advantage of the opportunities.

Most Compelling Opportunities and Impacts – 2015

- ***Further development of ^{225}Ac production technology:*** There has been significant progress made by the DOE Isotope Program in the development and production of some medically useful alpha-emitting isotopes in the past 5 years, but further research into new production methods, more efficient isolation methods, and automation of the isolation

processes is needed to provide adequate availability of alpha-emitting radioisotopes for preclinical and clinical evaluations. A focus should continue on production of ^{225}Ac and ^{211}At. DOE has developed a detailed project plan for ^{225}Ac, and this plan should be aggressively implemented.

- ***R&D for production of high specific activity theranostic isotope pairs:*** The move towards personalized medicine can be facilitated by supporting research on the production of radioisotopes, and isotopic pairs of the same element, that have both imaging and therapeutic emissions. A requirement for theranostic radioisotopes produced for medical use is that they have very low quantities of other isotopes of that element present (or "high specific activity") after production and isolation. Personalized medicine will use highly specific targeting of diseased cells in patients to differentiate their disease and help identify treatments that will be effective.

- ***Further utilization of University cyclotrons for research isotope supplies:*** The effort to form a network of university facilities that work with the Isotope Program is commended and should be continued. University facilities have the ability to cost-effectively augment the capabilities of the national laboratories, and to meet demands for radioisotopes and radioisotope R&D that are not possible at the national laboratories, such as regional production of short-lived radioisotopes (e.g. ^{211}At) and evaluation of some alternative methods for radioisotope production.

- ***Development of isotope production capabilities for FRIB:*** During routine operation for its nuclear physics mission, FRIB will produce a broad variety of isotopes that could be harvested synergistically without interference to the primary user. Research quantities of many of these isotopes, which are of interest to various applications including medicine, stockpile stewardship and astrophysics, are currently in short supply or have no source other than FRIB operation. R&D aimed at the feasibility of harvesting isotopes at FRIB is being supported by the Isotope Program and should continue.

- ***Exploration of electron accelerators for isotope production:*** One of the major driving forces for new radioisotope production R&D is the need for increased yield and high specific activity. One of the newer approaches is the use of photons to initiate isotope production. While the (γ,n) reaction is the most widely discussed, additional reactions could be examined, including (γ,p) and photofission.

Relationships of Existing and Future Capabilities – 2015

The relationships among existing DOE supported capabilities, enhanced utilization of existing capabilities, utilization of untapped capacity and the development of future capabilities have all been pursued aggressively by IDPRA since 2009. Many of the efforts are ongoing, and there is still significant opportunity for additional improvements and increases in capability. New opportunities will have to be considered in future planning, balancing additional capital investments versus better utilization of existing capabilities. Even with these considerations, the subcommittee has determined that additional capital investments are required and these are included in the priority recommendations.

- Existing Capabilities - DOE high-energy accelerators at BNL and LANL effectively coordinate schedules to extend availability. DOE also utilizes international high-energy accelerators. Ways of increasing collaboration and cooperation among production facilities should continue to be investigated. DOE has taken major steps toward developing relationships with university cyclotrons and developing production capabilities at these cyclotrons. Universities may participate in a network of accelerators coordinated by DOE or they may choose to remain independent suppliers of radioisotopes in their own right, or both. All approaches, as well as other approaches in between, are being explored by DOE in collaboration with universities.

- Enhanced Utilization of Existing Capabilities or Untapped Capabilities - DOE has devoted additional beam time and additional processing resources toward production of research isotopes at DOE facilities through their support of core R&D activities. To the extent that resources are available these core programs should be continued and expanded. DOE has incorporated Arronax into their supply chain for ^{82}Sr and increased target irradiations for commercial isotopes. Further utilization of international collaborators for commercial isotope supply so that DOE accelerator beam time can be redirected to research isotopes could be beneficial. All currently approved research projects have been awarded the beam time they needed at the DOE isotope production facilities at this time, but more such projects are needed. DOE has increased utilization of unused beam time at university cyclotrons and enabled R&D for additional availability of research isotopes.
- Future Capabilities - Future accelerator capabilities should be used to complement existing capabilities. The public/private partnerships could be a major source of accelerator beam time for research isotope supplies in the future. Alternate accelerator technologies for isotope production should be evaluated. Opportunities at FRIB should be realized as identified by R&D efforts.

Research Isotope Availability – Current State

Research isotope availability has improved markedly since 2009 for a variety of reasons including the major emphasis that DOE Isotope Program under the Office of Nuclear Physics management has placed on better utilization of DOE accelerator capabilities, increased collaborations with university cyclotrons, and increased collaborations with international partners for commercial isotope supply, so that additional beam time is available for research isotope production. Not surprisingly, there remain significant opportunities for enhancements and increases in availability. This will all be dependent on the resources available and priorities determined by the Office of Science.

Recommendations

Full text of the Recommendations was given in the Executive Summary. Below are the recommendations related to accelerator produced isotopes.

- **We recommend a significant increase of funding for Research and Development**
  - Increased R&D is essential for an optimal Isotope Program. Increased R&D is necessary to fully realize the promise of enhanced national security, improved health care, and increased industrial competitiveness the program could provide. It will also support the expansion of the range and quantities of isotopes available for researchers and for potential commercial application, and enhance their usefulness to the Nation. It will support the development of more efficient techniques for their production, reducing costs and ensuring that supplies meet demands. R&D is also a core component of the program, enabling it to better weather fluctuations in revenues (funding) as isotopes transition to the commercial market and as foreign supplies vary. In addition to establishing optimal base R&D funding at the production sites, the increase will facilitate annual (rather than biennial) Funding Opportunity Announcements (FOAs) to be issued, allowing the program to identify and respond more rapidly to new ideas. This increase will allow the program to effectively support promising new areas as they arise. Four representative areas that would benefit today from increased R&D support are:
  - ***Continue support for R&D on the production of alpha emitting radioisotopes***
  - ***Support R&D into the production of high specific activity theranostic radioisotopes***
  - ***Continue support for R&D on the use of electron accelerators for isotope production***
  - ***Support R&D on the development of irradiation materials for targets that will be exposed to extreme environments to take full advantage of the current suite of accelerator and reactor irradiation facilities***

  Details about each of these four areas are in the formal recommendations in the Executive Summary of this report.

- **We recommend an increase in the annual appropriated budget to realize the opportunities associated with high-impact infrastructure investments and to maintain a stable funding base for reliably operating and continually improving facilities. Specific opportunities for the period covered by this Long Range Plan include:**
  - ***Infrastructure for isotope harvesting at FRIB***.
  - ***Increase the base infrastructure budget to sustain and expand production capacity at the Isotope Program facilities. Two near-term opportunities that merit support from this increased funding are:***

    BNL Intensity upgrade and implementation of a second target station

    Intensity, stability, and energy upgrades at LANL.

  Again, details about each of these areas are in the formal recommendations in the Executive Summary of this report.

- **We recommend continuation and expansion of the effort to integrate the university facilities with the Isotope Program**

  The effort to form a network of university facilities that work with the DOE Isotope Program is commended and should be continued. University facilities have the ability to cost-effectively augment the capabilities of the national laboratories, and to meet demands for radioisotopes and radioisotope R&D that are not possible at the national laboratories, such as regional production of short-lived radioisotopes (e.g. ^{211}At) and evaluation of some alternative methods for radioisotope production. Partnership with university sites can also provide complementary and/or supplemental capabilities for production of isotopes where demands are not currently being met. The possibilities should continue to be evaluated on a site-by-site basis, in view of the differing capabilities of the universities. Several universities already provide radioisotopes that meet national needs, either by supplying commercial sources or making radioisotopes that are not readily available from commercial suppliers. Continuing exploration of how these university radioisotope producers can work with the DOE Isotope Program and how DOE could support university infrastructure and operations without compromising the Isotope Program or the current university production and distribution network is viewed as challenging, but very important, as coordination of this effort with the Isotope Program would improve the availability of key isotopes. Other university facilities do not yet produce isotopes in significant quantity and are likely to need improvements in infrastructure and equipment. The Isotope Program should continue to consider infrastructure upgrades to university facilities to produce isotopes to meet specific national needs. It is recognized that the degree of integration and the details of the interfaces of each university facility into the DOE Isotope Program will vary by site and circumstances. Finally, an important additional benefit of a DOE-university site partnership is the workforce training opportunity. It is recognized that these training opportunities are currently an important part of the Isotope Program and it is strongly recommended that they be continued.

Operations Roadmap

The 2009 NSACI recommendation for a dedicated accelerator for isotope production has been addressed by a Funding Opportunity Announcement (FOA) soliciting proposals on “Leveraging Isotope Program Resources and Enhancing Facilities” (including public/private partnerships), as well as cost-effective development of additional capabilities at university production sites. This is an appropriate response given budget constraints and the rapidly evolving commercial capability landscape.

6.C: Reactor Based Isotope Capabilities

Reactor Production of Radioisotopes

Many of the radioisotopes used for research, industry and medicine are produced through neutron induced nuclear reactions. Because neutrons have no electrical charge, they can penetrate into the nucleus of a target atom at very low energies and the probability of nuclear

reactions with low-energy neutrons is typically several orders of magnitude larger than reactions with charged particle beams. The other major difference between charged particle and neutron induced reactions is that a neutron source can irradiate many different targets at the same time to simultaneously produce multiple radioisotopes. The strength and versatility of neutron based isotope production is demonstrated by the fact that over seventy percent of the world's supply of the most used medical imaging isotope, ^{99}Mo, which is used in about 14 million investigations per year in the U.S., is provided by two research reactor facilities that simultaneously produce many other medical and industrial isotopes.

In nearly every case, the source of neutrons for isotope production is a research reactor. Unlike power reactors, which fission uranium as a source of energy to generate electricity, research reactors fission uranium to create the intense source of neutrons needed to produce neutron-rich radioactive isotopes. While neutrons can be produced by other types of nuclear reactions, only nuclear reactors provide the continuous intensity of neutrons needed to efficiently produce both the large quantities and high specific activity of isotopes through neutron-induced reactions.

The peacetime production of radioisotopes with reactors began in 1946 at the Graphite Reactor in Oak Ridge, TN with the production of ^{14}C that was sent to the Barnard Free Skin and Cancer Hospital in St. Louis, Missouri. During its first year of operation, the Laboratory made more than 1000 shipments of 60 different radioisotopes. Today, the use of reactor-produced isotopes touches upon nearly every field of science and technology as discussed in Chapter 3, including the oil and gas industry, explosives and narcotics detectors at airports, medicine, biochemistry, genetics and molecular biology.

U.S. Research Reactors

The United States currently has 32 research reactors licensed by the Nuclear Regulatory Commission (NRC) and 2 reactors operated by the U.S. DOE that are used for research and isotope production. Most of the research reactors in the country are over 40 years old; however, many have recently completed or are currently in the process of relicensing for an additional 20 years. Seventeen U.S. research reactors have power levels greater than one megawatt, and 3 of these are uniquely suited for isotope production: the University of Missouri Research Reactor (MURR), the High Flux Isotope Reactor (HFIR) at Oak Ridge National Laboratory, and the Advanced Test Reactor (ATR) at Idaho National Laboratory. Each of these has sufficient neutron flux and irradiations facilities to allow for the reactor production of radioisotopes. The fourth high-power research reactor (at NIST) does not currently produce isotopes.

The University of Missouri Research Reactor (MURR) operates at 10 megawatts with a peak flux of 6×10^{14} n·cm^{-2}·sec^{-1} and is the most powerful research reactor located on a U.S. university campus. MURR features multiple irradiation facilities covering a spectrum of neutron fluxes and geometries. MURR's weekly operating cycle makes it a key supplier of a broad range of radioisotopes for research, education, and industry. Because the reactor is at full-power operation 52 weeks per year, it is ideally suited to provide the short-lived human use therapeutic isotopes ^{153}Sm ($t_{1/2}$ = 1.9 d), ^{90}Y ($t_{1/2}$ = 2.7 d), and ^{177}Lu ($t_{1/2}$ = 6.6 d), which are used for bone cancer pain palliation, treatment of inoperable liver cancer, and treatment of inoperable progressive midgut carcinoid, respectively. MURR is also the primary Western hemisphere producer of the biological tracer radioisotopes ^{32}P, ^{33}P, and ^{35}S. In 2014 MURR produced 36

different isotopes and made 1175 shipments of radioisotopes to 7 different countries. Additionally, MURR is now engaged in three initiatives to become a domestic supplier of ^{99}Mo.

The Oak Ridge National Laboratory High Flux Isotope Reactor (HFIR) operates at 85 megawatts and provides one of the highest steady-state neutron fluxes of any research reactor in the world. HFIR's primary mission for the DOE Office of Basic Energy Sciences is for neutron scattering research and materials studies. HFIR provides a peak flux of 2.6×10^{15} n cm^{-2} s^{-1} and currently operates six 24-day cycles per year. The facility has 31 target positions in the flux trap and over 20 target irradiation positions of varying sizes in the reflector region. Originally designed to produce usable quantities of heavy actinide isotopes, HFIR, through the Isotope Program, is the sole Western hemisphere producer of ^{252}Cf. This is a critical isotope used in energy for oil exploration and quality control of nuclear fuel, in industry for mineral and cement analysis and bridge corrosion measurements, and in security for handheld contraband detectors and land mine detection. The other primary isotopes currently produced at HFIR are ^{63}Ni (for detection of explosives and narcotics), ^{75}Se (for quality control of welds) and ^{188}W/^{188}Re (for the treatment of cancer and arthritis). The operating schedule and high neutron flux of HFIR lends itself to research-quantity, high-specific activity isotopes and to the production of heavy actinides and longer half-life isotopes. However, because of its running schedule and other mission requirements, HFIR is not well suited for large-scale production of short half-life radioisotopes such as ^{99}Mo, ^{153}Sm and ^{177}Lu.

The Idaho National Laboratory Advanced Test Reactor (ATR) is designed primarily as a nuclear fuel and materials test reactor for the DOE/NNSA Naval Reactors program and the DOE Office of Nuclear Energy. Because of its high neutron flux and large volume of irradiation space, the ATR lends itself to isotope production as well. ATR can operate at 250 megawatts with a maximum flux of 1 x 10^{15} n·cm^{-2}·s^{-1} although the constraints of its materials irradiation mission typically require it to operate at lower power levels. Currently, ATR operates about 170 days per year with each cycle lasting approximately 50 days depending on the power levels required by the experimenters. Although not a primary mission, ATR is well suited to produce significant quantities of high specific activity isotopes for industrial and medical applications. The facility's production of ^{60}Co, which has many uses including sterilization of medical instruments, industrial radiography, food and blood irradiation and thickness gauges, was shut down in 2012 because of a target failure. With support of the Isotope Program, the ^{60}Co target has been redesigned and production of ^{60}Co at ATR has resumed. The facility is also scheduled to begin production of ^{238}Pu in 2016 for use in radioisotope thermoelectric generators as the principal power source aboard deep-space exploration vehicles.

Fourteen of the university research reactors (URRs) in the United States have a power level of 1 megawatt or greater. These smaller research reactors are important regional sources for small quantities of short-lived radioisotopes for research and industrial applications. They are able to produce and transport small quantities of industrial and environmental tracers like ^{24}Na (15 h), ^{41}Ar (1.8 h), ^{82}Br (1.5 d), and ^{133}Xe (5.2 d) at a much lower cost than the DOE reactor facilities and, by doing so, are able to generate modest revenue to supplement their budgets.

Reactor Production of Isotopes in the Future

The existing U.S. research reactors have the capability and capacity to meet almost all current and projected domestic isotope production demands. The three notable exceptions are ^{99}Mo, ^{137}Cs, and ^{90}Sr, which are currently produced by neutron-induced fission of ^{235}U. While the capacity exists to irradiate low-enriched targets of ^{235}U to produce the current domestic demand for these and other fission product isotopes, the infrastructure is not in place to process the irradiated targets using current chemical separation procedures. There is, however, significant work under way supported by DOE/NNSA to create alternative methods for ^{99}Mo production including new approaches to fission production. Whether ^{99}Mo will be produced via fission of ^{235}U in the future in the U.S. and whether the approach will allow for collection of other fission isotopes remains an open question at this time.

In addition to ^{99}Mo, ^{137}Cs, and ^{90}Sr, industry currently relies upon foreign research reactors for many radioisotopes that are, or can be, produced with existing U.S. research reactors. This approach is not driven by the lack of capability or capacity, but rather by the substantially lower cost of these isotopes from foreign government subsidized reactor facilities. The global nature of isotope production and use was never more evident than when the world's ^{99}Mo supply was disrupted in 2009 after a series of safety related shutdowns of foreign reactor production facilities. Given the fact that many of the isotopes used by the oil and gas and manufacturing industry currently come from Russian production facilities and the geopolitical uncertainty associated with this supply network, the Isotope Program is urged to continue their efforts in coordination of reactor isotope production. In addition, the program should continue to maintain a base level or operational support for readiness capability for reactor isotope production in the United States.

As stated earlier, most research reactors in the U.S. are more than 40 years old. With the aging of the URR's, the DOE created funding in the mid-1980s to support research reactors in acquiring upgraded operational instrumentation and equipment. As the original facility's technology became dated or obsolete, these funds have been essential in maintaining facility operations and safety. Figure 15 shows recent trends in DOE NE funding that directly support university research reactor functions; reactor fuel support and reactor infrastructure upgrades. While many of the U.S. research reactors have extended their operating horizon by another twenty years, it is unreasonable to expect that they can safely and reliably operate much beyond this. Long-range planning needs to begin now at DOE to develop a strategy for reactor produced isotopes beyond the life of MURR, HFIR, and ATR. New research reactors take decades of planning to build and make operational. There are currently no plans for replacement capability in the United States for reactor-produced isotopes.

Risks to Reactor-Produced Isotopes

There are two main risks to the availability of reactor-produced isotopes: the age of the facilities and coordination of U.S. sources of production and international sources of isotopes. To minimize the potential disruptions in the availability of reactor-produced isotopes in view of the

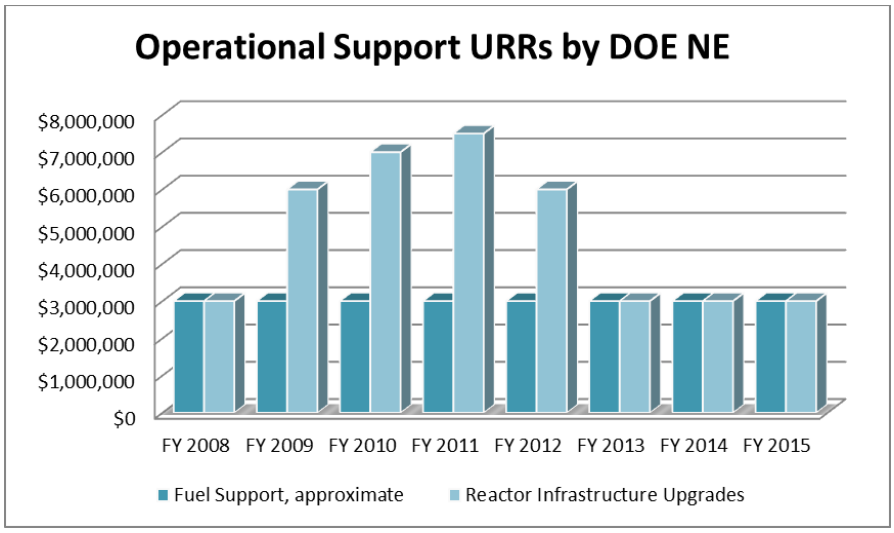

Figure 15: DOE NE funding in direct support of university research reactors

age of the three U.S. reactor facilities involved in isotope production (HFIR, ATR, and MURR) it is imperative that the Isotope Program:

- Continue coordinating with other offices within the Department of Energy who have stewardship and other responsibilities for these unique facilities to ensure their continued safe and reliable operation
- Develop a strategy for reactor isotope production beyond the life of MURR, HFIR and ATR

The second risk comes from the fact that other governments now view the isotope industry as a high tech growth industry and subsidize the production and sale of isotopes.

- The Isotope Program is urged to continue to support the OECD/NNSA effort to develop an international consensus and implementation of full cost recovery pricing for isotopes.
- The program should participate in efforts to maintain a base level of readiness capability for reactor isotope production in the United States consistent with its identified needs.

6.D: Isotope Production as a By-product of Other Operations

Introduction

Potentially important sources of isotopes for research, development, and industry are found in existing isotope stockpiles and irradiated targets which were produced by previous DOE programs and/or were byproducts of the programs. Most of these programs have ceased functioning or the DOE industrial complexes no longer have the capacity to produce isotopes. In addition, many of the feed-stocks used to produce these isotopes have been disposed and no longer exist. To produce these isotopes again in the amounts previously produced and in the current regulatory environment could require a multi-billion dollar investment and a very long lead-time. Consequently, the existing stockpiles are unique and invaluable and will most likely

never be produced again in these quantities. A number of years ago, DOE-EM conducted an inventory of isotopes present in the DOE complex. Some of the isotope inventory has been disposed of or is scheduled for disposal. However, significant amounts of very important isotopes remain in inventory, and some of these isotopes and their quantities are classified – consequently they cannot be discussed here.

The major stockpiles currently available are summarized in Table 13, and some information about their history and use are provided in Appendix 7. There are also a number of minor stockpiles available, including: mass-separated ^{233}U at ORNL (used to provide standard reference material); ^{227} Ac-at ORNL and PNNL (used for medical applications); ^{226} Ra-at ORNL and PNNL (used as a target for reactor production of ^{227}Ac and ^{229}Th); ^{232}U at PNNL and ORNL (used for medical applications); and mass separated ^{230}Th at ORNL (which is a potential target for production of ^{229}Th).

The DOE Office of Nuclear Materials Integration (OMNI) manages the DOE stockpiles of accountable materials. The DOE Isotope Program meets with OMNI on a monthly basis to discuss topics of mutual interest. No materials are disposed of without Isotope Program concurrence.

Table 13: List of existing major stockpiles

Major Stockpiles*
Mark 18 and Mark 42 at ORNL and SRNL
^{233}U: stockpiles at ORNL and INL,
Plutonium Isotopes: ^{244}Pu, ^{241}Pu, ^{239}Pu, and ^{238}Pu
Americium Isotopes: ^{241}Am (from decay of ^{241}Pu)
^{237}Np: target for the production of ^{238}Pu for NASA missions

* Additional details in Appendix 7

Types of isotopes available from existing stockpiles

The isotopes produced from these stockpiles and their applications are both diverse and very important for both basic and applied research. They include applications in medicine such as use of ^{225}Ac in targeted alpha therapy or ^{241}Am with many industrial applications such as use in smoke detectors. Table 14 summarizes the types of isotopes available from the stockpiles and their major applications. Most are available through the DOE Isotope Program. Further details are provided in Appendix 7.

Summary

These stockpiles of isotopes represent a precious resource for the Nation and result from major national investments. We recognize the potential major environmental concerns and costs associated with the continued storage and maintenance of these stockpiles, and the need in many cases for long-term solutions that would make isotope recovery impractical, but we urge that the

Table 14: Types of isotopes available from existing stockpiles*

Radioisotopes	**Major Applications**
$^{252}Cf/^{248}Cm$	Study of Physics and Chemistry of Cm
Heavy Cm	Preferred target for Production of ^{252}Cf
Light Cm	Proposed as target for production of heavy Cm
$^{241}Pu/\ ^{241}Am$	Many applications, widely used in smoke detectors
$^{237}Np\ /\ ^{233}Pa/\ ^{233}U/^{229}Th$	Std. reference material
$^{232}U/\ ^{228}Th,\ ^{224}Ra/^{212}Pb$ generator,	Medical applications
$^{231}Pa/^{227}Ac/^{227}Th/^{223}Ra$	Medical applications
^{229}Th, High Purity, Extracted from mass-separated ^{233}U	Std. reference material in geological studies
$^{229}Th/^{225}Ra/^{225}Ac$	Routine production of ^{225}Ac for medical applications
$^{90}Sr/^{90}Y$	Medical application and thermo-nuclear power sources
$^{44}Ti/^{44}Sc$	Medical application and thermo-nuclear power sources
$^{3}H/^{3}He$	Neutron detection, cryogenics, basic research

* Additional details in Appendix 7

unique nature of these isotopes be weighed heavily in the decision process. In particular, the great potential for alpha-therapy brings the ^{233}U situation to the fore, as a possible interim solution until other production can become available. There remains industrial need for ^{241}Am. The subcommittee is pleased to note that the importance of these resources seems well-recognized by the DOE Isotope Program. The Isotope Program has already obtained amounts of ultra-pure ^{233}U from the processing stream at ORNL and continues to consider cost-effective approaches for the extraction of additional ^{233}U. The Program is re-establishing a domestic production of ^{241}Am and supports the extraction of ^{3}He from tritium stockpiles. Many other isotopes from these stockpiles are available from the Isotope Program, which communicates regularly with ONMI on the availability and potential use of materials prior to disposition. We endorse the Isotope Program's participation in the NNSA MK-18 Interagency Working Group.

Recommendations

- **We recommend completion and the establishment of effective operations of the stable isotope separation capability at ORNL**
  - The subcommittee is pleased with the progress that has been made since the 2009 NSACI recommendation toward the establishment of a stable isotope separation capability. This ongoing effort should continue until the separation capability is fully established and available for routine use, providing a reliable U.S. source of high-purity stable isotopes, many of which are currently available only from Russia. That will require, among other things, the allocation of a base operations budget for the separator.
  - In addition, to improve the current state-of-the-art for isotope separations, investments will be necessary to improve the efficiency of isotope separators through development of low temperature ion sources and improved materials chemistry. The goal of this effort

should be to increase the throughput of the existing separator to be equivalent to at least that of one calutron (100 mA ion current).

- **We recommend realization of the opportunities associated with high-impact infrastructure investments. Specifically:**

  - ***Develop a strategy for the re-establishment of a separator for radioactive isotopes to support research*** – The isotope community has expressed the need for high specific activity, mass separated radioactive isotopes. A strategy for establishing a domestic capability for high purity radioactive isotopes should be developed. This capability is important to physical science programs, the medical community, and our national security. While chemical techniques can be used to separate the desired radioisotope from other elements, the selectivity to gain the isotopic purity desired by the community cannot be achieved without the development of electromagnetic separators for radioactive materials.

Chapter 7: Research and Development for Isotope Production

Our recommendations for research and development for isotope production are presented briefly in Sections A, B, and C of this chapter for stable isotope, accelerator, and reactor production respectively. In addition there are some R&D activities that apply across production techniques; they are summarized in section 7.D. A main focus of the R&D for production is on alpha-emitting isotopes and high specific activity theranostic pairs. This is driven by interest from researchers and clinicians for theranostic isotope-pairs. The development of new approaches for producing sufficient product becomes the primary challenge for moving toward clinical trials. In addition, we urge continued support and consideration for R&D on the use of electron accelerators for isotope production – a promising new approach, and R&D on targets exposed to extreme environments (both for accelerator and reactor production techniques) in order to take full advantage of the production capabilities of these facilities.

7.A: Stable and Radioactive Isotope Separation R&D

With the increasing interest in theranostic isotopes, there is a concomitant need to increase the availability through enhanced production. One of the major challenges for many of these isotopes is that the target materials are usually of low natural abundance so increasing the enrichment of these target materials will benefit the entire community. While many of the enriched materials are available from Russia, having a single foreign source is risky making the production of select elements for enrichment a high priority.

In addition, many of the theranostic isotopes are often made with accompanying isotopes of the same element. Thus a mass separator capable of separating radioactive species presents a very unique opportunity for obtaining the highest purity products for imaging and/or therapy. For example, the accelerator production of ^{225}Ac (10 d) contains ^{227}Ac (21 y). If the ^{227}Ac presents a problem with patient dosimetry, being able to isolate pure ^{225}Ac would be a tremendous advance.

- **We recommend an increase in the annual appropriated budget to realize the opportunities associated with high-impact infrastructure investments and to maintain a stable funding base for reliably operating and continually improving facilities. Specific opportunities for the period covered by this Long Range Plan include:**

  - ***Develop a strategy for the re-establishment of a separator for radioactive isotopes to support research*** – The isotope community has expressed the need for high specific activity, mass separated radioactive isotopes. A strategy for establishing a domestic capability for high purity radioactive isotopes should be developed. This capability is important to physical science programs, the medical community, and our national security. While chemical techniques can be used to separate the desired radioisotope from other elements, the selectivity to gain the isotopic purity desired by the community cannot be achieved without the development of electromagnetic separators for radioactive materials.

With the addition of the university based programs and the potential development of public/private partnerships, the need for capital expenditures to purchase a new cyclotron is difficult to justify. However for this more diverse approach to be effective the operating base of available facilities must increase and be coordinated to ensure availability on a routine basis.

There are clear challenges associated with developing agreements between DOE and universities needed to realize this diverse approach; in particular it will be necessary to clarify deliverables and university autonomy. Regardless, the inclusion of university production sites into the overall mission of making radioisotopes available for the user community makes it essential to find a working solution. Likely each university site will have to be considered on a case-by-case basis depending on the program in place at each site. The goal should be to form a network of university facilities that work with the Isotope Program. University facilities have the ability to cost-effectively augment the R&D capabilities of the national laboratories, and to evaluate some alternative methods for radioisotope production. Support for R&D at universities is already provided by the DOE Isotope Program through the competitive FOA's on Isotope R&D. Consideration should also be given to the provision of support for base R&D programs at university facilities

Chemistry for isolating desired isotopes

Faster, more efficient chemical separations will remain an important area of research, especially with the addition of new approaches to production coupled with the need/interest in new radioisotopes. Additionally, the development of automated approaches will be necessary to produce large quantities of these isotopes suitable for distribution.

New approaches for producing isotopes

Electron-linacs are becoming more prevalent, both in industry and academia. They represent a unique potential source of isotopes. While the highest production rates are for the (γ,n) reactions, the question is, can the use of the (γ,p) reaction overcome the shortcoming with low specific activity associated with neutron transmutation? This will require very high power machines and the development of chemistries associated with large target masses.

The isotope production scheme at FRIB is a potential new tool for the isotope community. The FRIB accelerator will produce high-intensity beams of heavy nuclei that react with a light target and produce a wide range of isotopes that can be separated, in-flight, by a magnetic device. The unused beam is stopped in a water beam dump. Extraction of isotopes produced in the water offers an opportunity for harvesting of interesting nuclides. The use of in-flight separation makes possible the collection of high specific activity samples. Thus FRIB could provide a fast path to research quantities of many isotopes and deliver isotopes otherwise difficult to produce. An example is ^{32}Si, discussed in Chapter 3. This isotope is typically produced by high energy protons in a KCl beam dump at the level of approximately 300 µCi per year. By acceleration of a ^{36}S beam FRIB could produce 100 µCi of ^{32}Si per day. Most research groups require about 10 µCi per year. The DOE Isotope Program is supporting R&D to determine the feasibility of harvesting isotopes from the future FRIB, and continued development of associated harvesting

and collection schemes to most efficiently use FRIB capabilities for the Isotope Program is necessary.

Challenges: low cross sections, high power targets

The primary metrics for radioisotope production are yield and purity. Yield is controlled by the cross section (probability of producing a particular product), the flux of beam (charged particles, neutrons, or photons), the target size and length of irradiation. In order to increase yields associated with increasing demand and, in some cases, to compensate for low cross sections, high beam power accelerators are being developed. Support of research into the development of smaller, higher-power facilities presents valuable opportunities. Such new approaches to isotope production will make DOE and the U.S. more competitive in the world marketplace. With higher power comes the primary issue of heat dissipation. Research into improving cooling and new target materials continues to be essential in order to continue meeting the demands for larger quantities of isotopes.

7.C: Reactor Production R&D

Two of our principle recommendations (1a and 1b) are directly relevant to research and development needed for the reactor production of isotopes:

- ***Continue support for R&D on the production of alpha-emitting radioisotopes –*** The lack of availability of alpha-emitting radioisotopes was identified in 2009 as a major limitation in the otherwise promising investigations of their potential for cancer therapy. Since the 2009 recommendation, the effectiveness of this novel therapy for cancer treatment has been demonstrated with FDA approval of the alpha emitter ^{223}Ra for metastatic bone cancer from hormone refractory prostate cancer. There has been significant progress made by the DOE Isotope Program in the development and production of some medically useful alpha-emitting isotopes in the past five years, but further research into new production methods, more efficient isolation methods, and automation of the isolation processes is needed to provide adequate availability of alpha-emitting radioisotopes for preclinical and clinical evaluations of this very promising therapy. A focus should continue on production of ^{225}Ac and ^{211}At. In addition, other alpha-emitting radioisotopes that may be applicable for treatment of other types of cancers, or for use in treating bacterial and viral infections are interesting. Thus, research into methods for production/isolation of alpha-emitters with shorter half-lives (e.g. ^{212}Pb/^{212}Bi, ^{213}Bi, and ^{226}Th) and longer half-lives (e.g. ^{227}Th) should also be a priority.
- ***Support R&D into the production of high specific activity theranostic radioisotopes –*** Medical procedures that can be tailored to an individual's unique response will be more effective and lower the cost of health care**.** The move towards personalized medicine will be facilitated by supporting research on the production of radioisotopes, and isotopic pairs of the same element, that have both imaging and therapeutic emissions. Such agents, termed theranostic agents, can be used to obtain valuable pharmacokinetic and disease-targeting information in real time, which can allow rapid determination of whether the therapeutic approach will be effective in a specific patient. A requirement for theranostic radioisotopes produced for medical use is that they have very low quantities of other isotopes of that element present (or "high specific activity") after production and isolation. Personalized

medicine will use highly specific targeting of diseased cells in patients to differentiate their disease and help identify treatments that will be effective. High specific activity radioisotopes are required so that the targeted receptor or cell-surface antigen on the diseased cells are bound with targeting agents containing only, or mostly, the theranostic radioisotope. If low specific activity radioisotopes are used, the disease-targeting agent containing a stable isotope (or non-useful radioisotope) can compete for the receptor or antigen, dramatically decreasing binding of the isotope that provides the diagnostic and/or therapeutic emissions. This can lead to inconclusive imaging results and ineffective therapy, resulting in an unsuccessful personalized medicine approach.

7.D: Other Production-Related R&D

In addition to R&D focused on specific isotope production techniques, there are other opportunities in areas such as processing and transportation that impact multiple isotope production techniques. There is an important opportunity in the development of post-irradiation methods for increased specific activity. Obtaining high specific activity will make the isotopes more useful in some applications.

There are major challenges with packaging & transportation associated with delivering irradiated products to internal or external processing facilities. While the issue of packaging is not under DOE's control, there is benefit in establishing a coordinated effort at bringing together the parties whose duty is to assure safety in transporting these products between facilities. Since 2009, the Isotope Program has added transportation expertise to the NIDC staff to address challenges within the program and has established a Transportation Working Group. These efforts have been beneficial and should continue.

To state the obvious, there needs to be a continued effort to provide research opportunities for basic research in isotope production and for directed research areas as they become obvious in this quickly changing landscape. Some of these will be in production R&D. The Isotope Program has an outstanding record of identifying important new areas for R&D as the field evolves, and it is essential that this be continued and expanded. Indeed, our first overall recommendation is that there be ***a significant increase in funding for Research and Development*** to further optimize the Isotope Program and its impact on the Nation.

Chapter 8: Trained Workforce and Education

Isotope production is a specialized area of scientific and technical advances. For this reason, it requires a highly trained workforce composed of individuals from various subspecialties including:

Nuclear chemistry is using chemical techniques to study nuclear properties and nuclear reactions. Knowledge in nuclear chemistry is imperative in isotope production, as it is needed to understand the nuclear reactions that are used to prepare a radioisotope. Importantly, an understanding of nuclear chemistry is required to advance the field through development of new methods for producing radioisotopes.

Radiochemistry is the specialized application of procedures and techniques common to chemistry involving radioactive elements and molecules. Knowledge in radiochemistry is required to safely handle radioactive materials. Knowledge in this field is also required to conduct or develop methods for identification, isolation and purification of isotopes, and radiolabeling of molecules with those isotopes.

Nuclear Pharmacy is a specialty area of pharmacy practice dedicated to compounding, quality control and dispensing of radiopharmaceuticals for use in positron emission tomography (PET) and single photon emission (SPECT) nuclear medicine imaging procedures, and for therapeutic applications. These specialists have advanced training and experience in these areas, and are able to facilitate diagnosis and consult on health and safety issues concerning radiopharmaceuticals, non-radioactive drugs and patient care. Specialists with this training are important for the production of isotopes that are going to be incorporated into radiopharmaceuticals for human use. Nuclear pharmacists help to improve and promote public health through the safe and effective use of radiopharmaceuticals for both diagnosis and therapy

The Workforce Pipeline and Historical Context

The practice and development of isotope production is primarily driven by individuals trained in nuclear and radiochemistry. The near-term workforce demands of the field can be met in part by individuals with advanced degrees in other areas (*e.g.* inorganic chemistry and nuclear engineering) who receive on the job training. This approach will only fill gaps in expertise in the short term, as it does not provide the same quality of preparation and expertise as an advanced degree in nuclear and radiochemistry. As early as the 1940s, our Nation recognized the critical need for research and education in these areas. Generous funding was provided by the government to universities for both research and the development of highly trained young scientists in nuclear and radiochemistry. Fellowships were instituted to attract the best and the brightest into these fields. The fields thrived, information needed to support our national interest was developed and, perhaps most importantly, a pipeline of highly trained scientists was created to secure the future. This is no longer the case and the education of trained professionals in nuclear chemistry and radiochemistry has been a matter of concern for many years.

In 1978, a committee established by the American Chemical Society (ACS) Division of Nuclear Chemistry and Technology (DNCT) surveyed both the status and future needs and supplies of workforce in nuclear and radiochemistry in the United States [ACS78]. The survey concluded

that 1) the numbers of nuclear and radiochemistry faculty members were decreasing, 2) there were few practicing radiochemists, 3) negative public perception had led to students' reluctance to enter the field, and 4) the supply of students trained in these and related areas fell far short of meeting the projected national needs.

Unfortunately, the decline in educational opportunities in nuclear and radiochemistry continues thirty-seven years after the ACS DNCT drew attention to the matter in 1978. The 2007 National Research Council study that reviewed the health of the U.S. chemical research community reported that although the United States still leads chemical research worldwide, its dominance in radiochemistry is being challenged as the number of U.S. chemistry departments offering a specialization in nuclear chemistry has decreased continuously over the past 30 years [NAS07]. In 2008, the American Physical Society (APS) Panel on Public Affairs Committee on Energy and Environment reported on the "Readiness of the U.S. Nuclear Workforce for 21st Century Challenges" [APS08]. An excerpt from the executive summary states "If nuclear chemistry and radiochemistry education programs are not reinvigorated, the U.S. will lack the expertise required to pursue promising advanced research and development in a myriad of disciplines." In the area of nuclear medicine, the 2007 NRC report "Advancing Nuclear Medicine Through Innovation" [NAS07A] concluded that "it is essential to reach out to chemistry students at the undergraduate and graduate student levels to fill the pipeline and avoid an impending generation gap in leadership in radiopharmaceutical chemistry." Given the continued erosion in educational opportunities, it is not surprising that the 2012 NRC report "Assuring a Future U.S.-Based Nuclear and Radiochemistry Expertise" [NRC12] found that the demand for Ph.D. nuclear and radiochemists over the next five years (~300) would greatly exceed the projected supply. The Isotope Program is to be highly commended for its positive impact on workforce training in an area where the Nation currently produces such a limited number (~15) of Ph.D. graduates per year. Over the last five years, research funding from the Isotope Program has supported the training of 45 nuclear and radiochemistry Ph.D. students and 33 post-doctoral fellows, and 120 undergraduate students have participated in isotope-related activities. Additionally, opportunities exist for students to participate in internships at several of the national labs.

In recent years, one of the most successful programs is the Nuclear Engineering Science Laboratory Synthesis (NESLS) [NESLS15], which is sponsored by the U.S. Department of Energy and is managed by the Oak Ridge Associated Universities' (ORAU) science education programs. NESLS is a cooperative research initiative geared toward students working in nuclear engineering and nuclear science. Through one- to three-year summer internships, NESLS offers students on-the-job educational and research opportunities at a multidisciplinary national laboratory. NESLS goals include maximizing the abilities of students through cooperative research with mentors at a national laboratory; increasing research opportunities; providing a learning environment useful to both national laboratories and students; and training next generation nuclear scientists.

One of the principal reasons given in the 2012 NRC report for the current and projected nuclear and radiochemistry workforce shortage is that "there is little nuclear and radiochemistry taught at the undergraduate and graduate level."[NRC12]. Table 15 summarizes the current situation. An excellent example of a program that has helped supplement inadequacies in undergraduate education is the DOE-sponsored ACS Division of Nuclear Chemistry and Technology Summer Schools in Nuclear and Radiochemistry (SSNR) (see Sidebar 13). The SSNR is an intensive

Sidebar 13: DOE Sponsored Summer Schools in Nuclear and Radiochemistry, Academic Centers and the Future Workforce

While the Summer Schools in Nuclear and Radiochemistry (SSNR) can recruit bright young talent to the field, it is important to recognize the importance of maintaining strong university programs in nuclear and radiochemistry. Despite the diverse range of careers that require skills in nuclear and radiochemistry, there are very few academic programs that offer undergraduate and graduate courses in these areas (Table 15). In the majority of undergraduate chemistry programs, these topics are never introduced or only briefly touched upon as the last topic in the first-year chemistry course. As a result, most of this nation's undergraduate science and engineering majors are never exposed to this critical area of chemistry.

An example of the importance of the SSNR and support of university programs by DOE NP is Daniel Stracener, PhD. From 1983 to 1986, he attended McNeese State University in Lake Charles, LA and graduated with a bachelor's degree in Chemistry. Up through his junior year he planned to be an organic chemist and thought he would work in one of the many refineries and chemical plants along the Gulf coast in Louisiana and Texas. As a junior, he was one of 12 students accepted to participate in the 1985 ACS Nuclear Chemistry Summer School that was held at San Jose State University. *"This wonderful and life-changing experience was an intense 6-week course that introduced me to nuclear chemistry and radiochemistry. During the course we were privileged to meet and learn from several distinguished scientists, including Glenn Seaborg, Darlene Hoffman, and Michael Welch. Based on my experience at this summer school, I decided to apply to graduate school to pursue a degree in radiochemistry and was accepted to Washington University in St Louis."*

Upon his arrival, he decided to work with a group led by Demetrios Sarantites and Lee Sobotka. He was awarded the Arthur C. Wahl scholarship and had the privilege of interacting with him for almost four years during his graduate studies. Dan graduated in 1993 with a Ph.D. in Nuclear Chemistry from Washington University in St. Louis and went to Oak Ridge National Laboratory (ORNL) as a post-doc in the Physics Division.

In recent years, his research has moved to a field in which his interest was first stimulated at the Nuclear Chemistry Summer School and he has become involved in the production of radioisotopes for medical purposes. This started with a project to measure proton-induced cross-sections for the production of ^{229}Th using relatively low energy proton beams. This isotope is long-lived and decays to ^{225}Ac, an important radioisotope for cancer therapy as discussed in Chapter 3. Other projects now include the production of ^{227}Ac at ORNL and a collaborative effort by three DOE laboratories to develop a production process for ^{225}Ac using high energy proton beams.

Sidebar 13 (cont.)

Table 15: Graduate Programs in Nuclear Chemistry and Technology. The list includes related programs that reside in nuclear engineering departments [Nucl-ACS]

Auburn University	University of Maryland, College Park
Colorado School of Mines	University of Missouri, Columbia
Clemson University	University of Nevada, Las Vegas
Florida State University	University of Notre Dame
Hunter College, CUNY	University of Pittsburgh
Indiana University	University of Rochester
Michigan State University	University of Tennessee, Knoxville
Oregon State University	University of Texas, Austin
Stony Brook University	University of Utah
Tennessee Technological University	University of Washington
Texas A&M University	Washington State University
University of Alabama	Washington University, St. Louis
University of California, Berkeley	

6-week undergraduate fellowship program designed to introduce nuclear and radiochemical concepts through lecture and laboratory experiments to outstanding upper level undergraduate science and engineering majors and to stimulate their interest to pursue graduate studies in the field. SSNR targets undergraduates, and it has served as a critical pathway for filling the graduate student pipeline to develop and train the next generation of nuclear and radiochemists.

For three decades, the DOE has funded the SSNR. Since the first course in 1984, the Summer Schools have successfully introduced 675 of this Nation's best and brightest undergraduate students to nuclear and radiochemistry and provided information on summer internships at national laboratories, graduate education, and career paths in these fields. Nearly 20% of all the Summer School participants have gone on to pursue careers in the nuclear sciences and many of these individuals are now in a position to influence other young people to enter the field. The impact and importance of the Summer Schools on graduate and postdoc workforce training in this area is highlighted by the fact that approximately half of the 15 to 20 nuclear chemistry and radiochemistry Ph.D. degrees now awarded annually in the United States are to individuals who were introduced to the field through the Summer Schools in Nuclear and Radiochemistry. The SSNR has received funding through summer 2015 and we strongly recommend that the Isotope Program continue to work with other DOE offices to continue this highly successful program for 2016 and beyond.

The DOE Isotope Program has supported several university sites for both research and routine isotope production activities. It is important to note that these funds often support trainees involved in research at the undergraduate, graduate and postdoctoral level. In many cases, the research projects form the basis of a PhD thesis project in nuclear or radiochemistry, biomedical engineering or medical physics. The DOE Isotope Program has also been active in sponsoring travel awards for students to present their findings at scientific conferences. These activities are commendable and should be continued.

Recommendations

Recommendation 7 of the 2009 NSACI Long Range Plan was focused at developing a highly trained workforce for the future. Specifically, it recommended that the Isotope Program: ***"Invest in workforce development in a multipronged approach, reaching out to students, post-doctoral fellows, and faculty through professional training, curriculum development, and meeting/workshop participation."*** In recognition of the improvements to the overall program, and specifically to workforce development, since 2009, we have not made a specific formal recommendation in this report. Rather, we have simply noted in our Operations Roadmap (in Section 9.C) that the Isotope Program has made dramatic improvements since the 2009 NSACI Long Range Plan, and it is essential that the practices, procedures, and key programs put in place continue. One of the key areas where continued emphasis will be essential for continued progress is workforce development. Specifically:

> Investments in workforce development to educate and train the next generation of nuclear scientists focused on isotope production should continue to be a priority. Funding university programs at the undergraduate, graduate and postgraduate levels enable a highly trained workforce and can also generate new technologies and ideas. Support for junior faculty research funding through programs such as the DOE Early Career Awards enhances the prospects for permanent faculty engaged in isotope research (and the subsequent involvement of students). Finally, in response to the decline in undergraduate educational opportunities in the field of nuclear and radiochemistry and concomitant lack of student exposure to the field, the Isotope Program is encouraged to work closely with other DOE-SC programs to expose outstanding undergraduate science and engineering majors to nuclear science and radiochemistry.

We note also that our formal recommendation for "***the continuation and expansion of the effort to integrate the university facilities with the Isotope Program"*** has as one of its principle motivations and benefits the recruitment and training of the worforce so essential for the field.

Chapter 9: Program Operations

In this chapter we begin with a summary of the situation in 2009 when the program was transferred to the Office of Nuclear Physics and the first NSACI Reports were written. This is followed by a discussion of the evolution of the program to today and our judgment on how well IDPRA has responded to the recommendations of those reports (both the Long Range Plan and Research Opportunities). Finally, we identify challenges and opportunities associated with budget levels we will recommend.

9.A: The Program in 2009, Its Evolution Since Then, and Its Status Today

Historical Background

Isotopes, both stable and radioactive, are the foundation of multi-billion dollar per year industries, including health care, aircraft manufacture, oil exploration, and others. The economic benefits that derive from these industries have their origin in the research and development and production capabilities that were established during the Manhattan Project, and nurtured during the development of the Atomic Energy Commission (AEC). The Atomic Energy Act of 1954 was the enabling legislation that established the peaceful use of nuclear energy, including the use of isotopes, as a mission focus of the AEC National Laboratories. The National Laboratories have continued the research and development, and the support of availability of these materials to the present time. However, isotope production and R&D has always been a secondary mission for the national laboratories, and the facilities and infrastructure that support isotopes is dependent on the health and vitality of the national laboratories primary missions.

Research and Development: Research into the production and applications of isotopes has been an on-going, albeit secondary mission of the national laboratories since their inception during the Manhattan Project or after. After production technologies were established, these isotopes were made available to researchers external to the National Laboratories. Usually, applications were developed in a collaborative way between national laboratory researchers and university or industrial researchers. Tragically, these types of collaborations were no longer possible since the 1990s and before 2009, because the national laboratories no longer had access to funding to support these collaborative efforts.

Production: In the early days of the AEC, isotopes were made available in the collaborative way described above, and this ready availability supported the successful transfer of technology from the national laboratories to the private sector, and the development of the industries mentioned above. In 1989, Public Law 101-101 was enacted, with the goal of making DOE's isotope production and distribution efforts financially self-sufficient. Although the goal is laudable, we are now almost 25 years into this experiment, and experience suggests that it is a significant challenge for DOE's isotope production activities to recover costs for the variety of isotopes that DOE's research constituencies require, due, in part, to the high cost of doing business within the National Laboratory complex. In fact attitudes about DOE's isotope production and distribution efforts had become extremely negative among the customer base after this change in 1990. However, as indicated below much has changed since the program was moved to the Office of Science, Office of Nuclear Physics in 2009. The following sections

of this chapter detail many of the positive changes and improvements that have been accomplished since 2009.

DOE Requirements for Isotopes: DOE has its' own intramural isotope needs, and traditionally the National Laboratories have satisfied these needs. This remains the case today. DOE requirements for isotopes can be found in the areas of national defense, homeland security, space applications, environmental science, nuclear technology applications, and fundamental science. In many cases these requirements are too sensitive to be left to domestic commercial suppliers or foreign sources. Domestic production capabilities are the best and most secure way to satisfy these requirements, which are assessed annually through the Workshop on Isotope Federal Supply and Demand that the Isotope Program organizes. Most of the isotopes needed (with the exception of accountable materials for defense work) are provided through the Isotope Program.

Pricing of Isotopes: The Isotope Program operates under a revolving fund established by the 1990 Energy and Water Appropriations Act (Public Law 101-101), as modified by Public Law 103-316. Each isotope is priced such that the customer pays the cost of production. Commercial isotopes are sold at full-cost recovery. The Energy and Water Development Appropriations Act (Public Law 101-101) of 1990 requires that "fees shall be set by the Secretary of Energy in such a manner as to provide full cost recovery, including administrative expenses, depreciation of equipment, accrued leave, and probable losses." The revolving fund was established so that the revenues received from the sales were available for production and related activities without further appropriation. In 1995, Public Law 103-316 stated "fees set by the Secretary for the sale of isotopes and related services shall hereafter be determined without regard to the provisions of Energy and Water Development Appropriations Act (Public Law 101 -101)." This law, in principle, gives broad latitude to DOE in determining pricing policy.

Withdrawal of the DOE Program from commercial markets for a particular isotope: DOE adheres to the procedures and criteria expressed in the Federal Register, Tuesday, March 9, 1965, with respect to determinations involving its withdrawal and re-entry into commercial markets. These include reasonable and consistent prices, but allow a federal position in the market in the case of some single source or foreign producers. Under these procedures, private industry may petition the government to withdraw from a competitive market. In general, it is the policy that the federal government does not compete with private industry unless dominant national interests are determined to be involved.

For a detailed description of the state of the Isotope Program in 2009 see the two 2009 NSACI reports [NSACI09, NSAC09A]. When the program was moved from the Office of Nuclear Energy to the Office of Science in 2009, the DOE Office of Science asked the Nuclear Science Advisory Committee to review the state of the program and to suggest recommendations for immediate and longer-term actions to effect improvements in program performance. The recommendations from the first NSACI subcommittee are summarized below.

The Recommendations of the 2009 NSACI:

Report I [NSACI09] on Compelling Research Opportunities made six recommendations:

1. Invest in new production approaches of alpha-emitters with highest priority for ^{225}Ac. Extraction of the thorium parent from ^{233}U is an interim solution that needs to be seriously considered for the short term until other production capacity can become available.
2. We recommend investment in coordination of production capabilities and supporting research to facilitate networking among existing accelerators.
3. We recommend the creation of a plan and investment in production to meet these research needs for heavy elements.
4. We recommend a focused study and R&D to address new or increased production of ^{3}He.
5. Research and Development efforts should be conducted to prepare for the reestablishment of a domestic source of mass-separated stable and radioactive research isotopes.
6. We recommend that a robust investment be made into the education and training of personnel with expertise to develop new methods in the production, purification, and distribution of stable and radio-active isotopes.

Then Report II [NSACI09A], the Long Range Plan for the (then) present progam, made nine recommendations for improving the program.

Six were for operations processes:

1. Maintain a continuous dialogue with all interested federal agencies and commercial isotope customers to forecast and match realistic isotope demand and achievable production capabilities.
2. Coordinate production capabilities and supporting research to facilitate networking among existing DOE, commercial, and academic facilities.
3. Support a sustained research program in the base budget to enhance the capabilities of the Isotope Program in the production and supply of isotopes generated from reactors, accelerators, and separators.
4. Devise processes for the Isotope Program to better communicate with users, researchers, customers, students, and the public and to seek advice from experts.
5. Encourage the use of isotopes for research through reliable availability at affordable prices.
6. Increase the robustness and agility of isotope transportation both nationally and internationally.

One aimed at developing a highly trained workforce for the future:

7. Invest in workforce development in a multipronged approach, reaching out to students, post-doctoral fellows, and faculty through professional training, curriculum development, and meeting/workshop participation.

and two were on major investments in production capability:

8. Construct and operate an electromagnetic isotope separator facility for stable and long-lived radioactive isotopes.
9. Construct and operate a variable-energy, high-current, multi-particle accelerator and supporting facilities that have the primary mission of isotope production.

In the next section we acknowledge the tremendous progress that has been made in the evolution of the program. Sidebar 14 summarizes the evolution of the production sites during this period. Appendix 9 provides a detailed list of the steps and actions that have been taken with respect to the implementation and execution of the 2009 recommendations. In every instance the Program has generated a successful outcome of the recommendation or is well on the way to success in the future.

9.B: Evaluation of the Program and Its Evolution Since 2009

As stated previously, the Program has made tremendous strides since the move to the Office of Science in 2009. Noteworthy changes include a new emphasis on research and development, investment and refurbishment of major infrastructure enabled by the American Recovery and Reinvestment Act (ARRA) funding, and improved focus on availability of research isotopes while maintaining reliability in the distribution of commercial "niche" isotopes. Here we summarize some of the major changes made under the management of the Office of Nuclear Physics to program operations since 2009, the response to the recommendations from the 2009 reports, and the Subcommittee's evaluations of those responses and their effectiveness.

Summary of changes in program operations since 2009

A new management organization has been created within the Office of Nuclear Physics (IDPRA, and under it the NIDC).

Production facilities have been upgraded, and the suite of facilities in the portfolio expanded, with selective supply from six universities. Sizable investments have been made in production facility infrastructure to refurbish aging equipment and to expand production capabilities.

Investment in isotope-related research has been more substantial and more regular in the past five years, both to the national laboratories and via competitive awards to universities and national laboratories.

In FY13 the total budget for the Isotope Program was $56.4M, including $18.5M from appropriation and $37.9M from sales. The latter is more than twice as large as it was five years earlier, reflecting the increase of scope of the program and effective operations. A large fraction of the sales involve ^{82}Sr, an isotope that could be commercialized in the future. This could eventually have a significant impact on the sales budget of the DOE Isotope Program, but it is difficult to be sure of the time scale and scope of the impact. Stabilization of the Isotope Program against major fluctuations in the overall budget and R&D toward preparation for the next major sales isotope are important considerations of this Long Range Plan.

Isotope pricing has been assessed and made more consistent. Comprehensive bottom-up cost studies for isotope production were developed for all activities at the sites in the program.

The Isotope Program has updated and documented all of its pricing policies and rationale. Research isotopes are now identified by their application, which is submitted by the customer for assessment by Isotope Program staff. If the isotope request is approved as a research isotope request, then it may be sold at the subsidized research price, which includes only direct

Sidebar 14: Evolution of the Isotope Program

Isotope Program operations have evolved significantly under the management of the Office of Nuclear Physics as detailed throughout Chapter 9. Nowhere is this more evident than in the marked changes that have occurred with availability of research isotopes and the number of sites the DOE Office of Science has involved in isotope production and distribution since they became responsible in 2010. The two figures below demonstrate this change dramatically. Before 2009, the DOE basically depended on their national laboratory facilities to provide both commercial "niche" isotopes and research isotopes. Since 2009, DOE has expanded their approach significantly, and now as many as 13 sites are engaged in production and distribution either directly for or in collaboration with the DOE program.

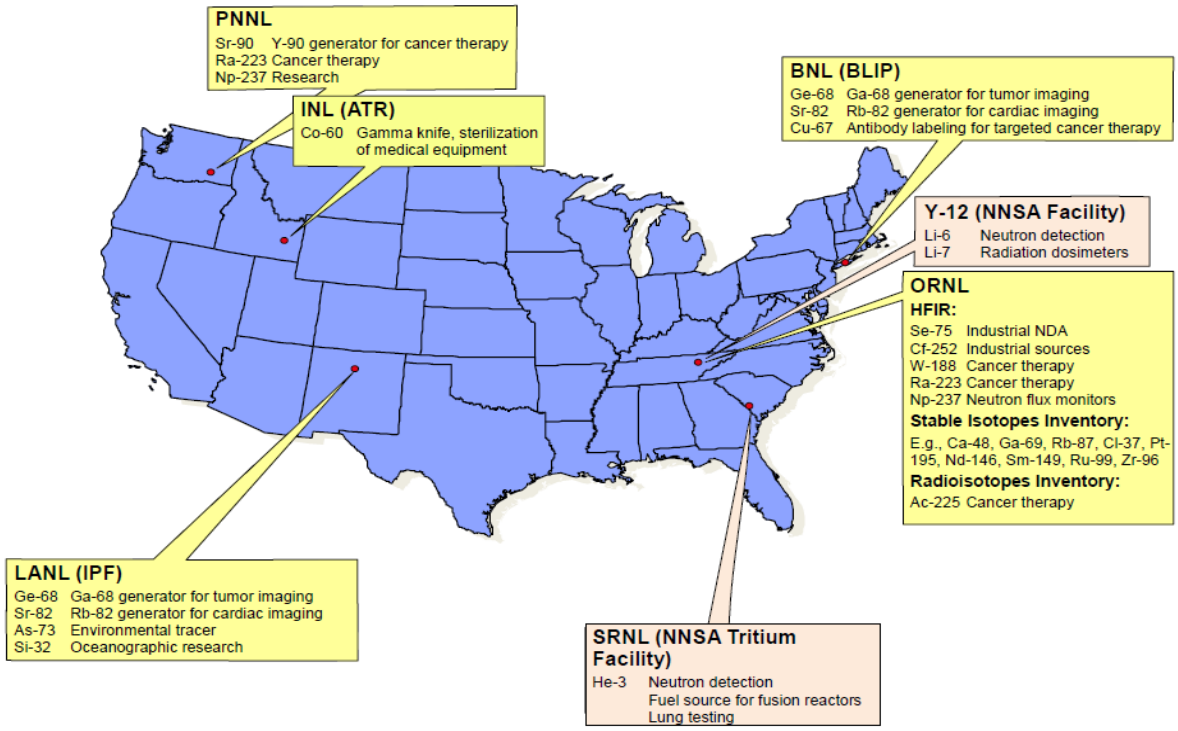

Figure 16: Isotope Production Sites Circa 2009

Additional University accelerator facilities could contribute greatly to the availability of research isotopes. They already have proven track records for significant quantities of research isotopes including ^{64}Cu, ^{44}Sc, ^{86}Y, ^{76}Br, ^{77}Br, and ^{72}As. Recent DOE investments at Washington University and the University of Wisconsin have led to increased availability of ^{64}Cu and ^{89}Zr. The addition of the University of Washington and Duke University has the potential of expanding the availability and use of ^{211}As, which is an α-emitting isotope that the 2009 NSACI report highlighted in its research opportunities recommendations. Expanding the University collaborations program further will yield opportunities for availability of other research isotopes, and also enhance availability of the isotopes discussed above.

Sidebar 14 (Cont.)

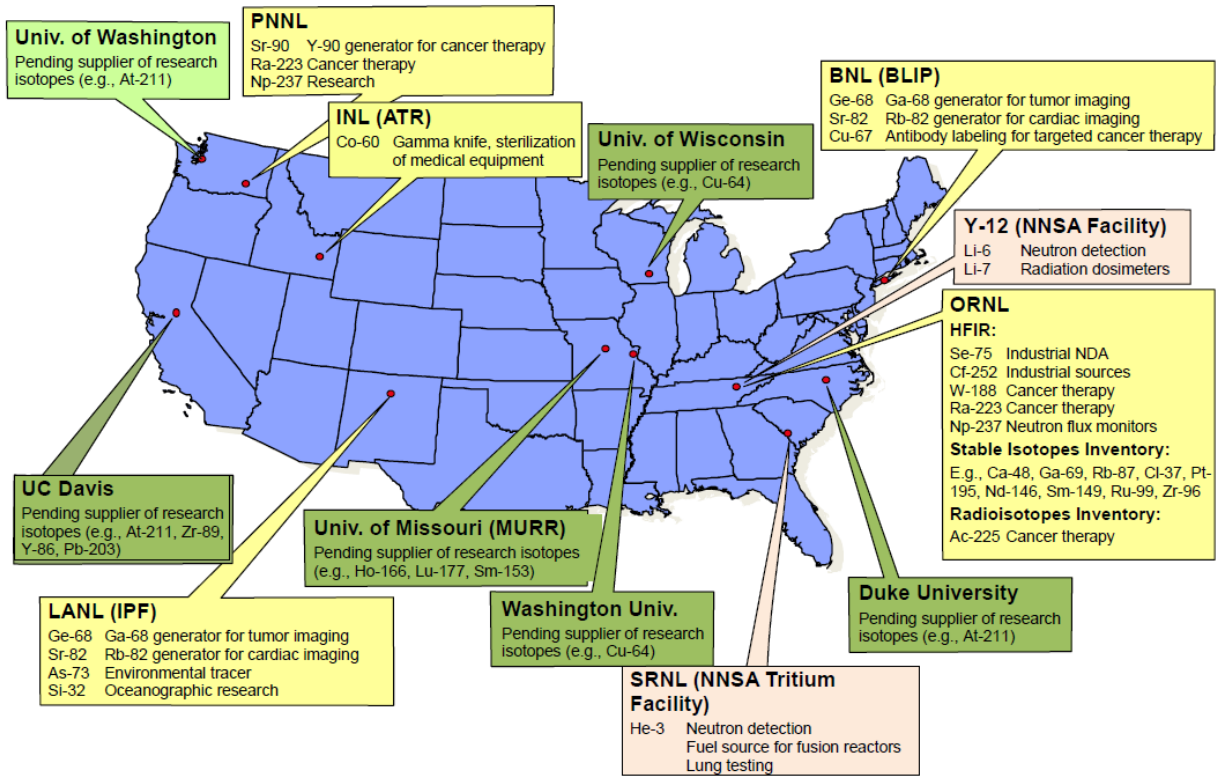

Figure 17: Isotope Production Sites and Affiliated University Sites Circa 2015

Another benefit that DOE derives from expanding their University collaborations is that they expand the availability of research isotopes without limiting accelerator capacity at their National Laboratory sites for additional R&D, as well as production capability for the commercial "niche" isotopes that generate much needed revenue for the Program.

Thus it is clear that DOE implementation of the 2009 recommendation to incorporate University cyclotrons into their network or through collaborations has been of great benefit to those Universities that collaborate, and it has also benefited the DOE program by expanding research isotope availability and extending the capability of their existing accelerator network. For these reasons this long range plan encourages the continued collaborations with existing facilities and expansion to other University accelerators where possible.

production costs. In addition, the research isotopes are sold by unit price as opposed to batch price. As research isotope applications often require small amounts of isotopes, it can become cost-prohibitive if the customer must pay for the production of an entire batch, irrespective of whether the batch quantity is needed. If the full batch is not needed, the Isotope Program bears the cost of producing the full batch, should the remaining material not be sold. These actions have made research isotopes more affordable to the community. In addition, since 2009 the Isotope Program has implemented robust and effective financial auditing processes in order to verify the Program accounting, costing and pricing approaches. A pricing memo is issued annually.

Enhanced communication with isotope customers has been developed in a variety of ways. Improved communication on isotope needs and issues with other federal agencies has occurred in recent years through workshops and interagency working groups.

Evaluations have been made on commercialization requests by private suppliers. Since 2009, the Isotope Program has assessed, developed and documented all steps associated with the implementation of the procedures and criteria expressed in the Federal Register. The Program has had the opportunity to implement those procedures, which led, for example, to its partial exit of the ^{68}Ge market and its re-entry into the market for ^{212}Pb/^{212}Bi generators.

Appendix 9 provides a summary of the recommendations from the 2009 NSACI reports and the details of the Isotope Program's responses to and actions on these recommendations. It was provided to NSACI (at our request) by the Isotope Program and reviewed by the subcommittee.

Evaluation of the Responses to the Recommendations

In summary, the subcommittee finds that the Isotope Program has addressed all of the recommendations for operations that were made in the 2009 NSACI reports.

The subcommittee commends the DOE program management for the logical and straightforward way that they have addressed each recommendation both tactically and strategically. The 2009 NSACI subcommittee recognized at the time the tremendous amount of work that they were committing program management to perform with the large number of recommendations that were put forward. The significant numbers and breadth of the recommendations were necessary to realize the tremendous potential of the program to improve multiple segments of U. S. society ranging from health care and industrial competiveness to national security. The Program has made great strides and is far better positioned for continued success in the future compared to 2009. In the next section we acknowledge areas where, while progress has been made or is ongoing, and activities are on a positive trajectory, there are still opportunities for improvement. As new recommendations and opportunities are tackled, the subcommittee wants continued vigilance to maintain the improvements and momentum realized to date.

Specifically, recommendation 9 of report II (NSACI09A) that the Program "Construct and operate a variable-energy, high-current, multi-particle accelerator and supporting facilities that have the primary mission of isotope production" was particularly difficult given the funding environment over the past six years. The original recommendation was offered in an attempt to develop flexibility and reliability in research isotope availability by having a facility dedicated to that mission. DOE is attempting to accomplish the spirit of this recommendation and impact research isotope availability through their encouragement of public/private partnership initiatives and through their support of the University initiatives. Successful development of these approaches will accomplish results that will be similar to what would have been possible with the construction of a dedicated accelerator facility.

9.C: Recommendations for Its Continued Enhancement

Our intention in this section is to capture the main points of "continue the good work" discussed as part of the subcommittee's deliberations, and to identify important areas of real progress

where continued improvement will require continued effort. These activities are listed below in what we are referring to as an "Operations Roadmap".

Operations Roadmap

The Isotope Program has made dramatic improvements since the 2009 Long Range Plan as described above, and it is essential that the practices, procedures, and key programs put in place continue. Key areas where continued emphasis will be essential for continued progress are:

Communication: Continued excellence in communication will enable the program to nimbly respond to the diverse isotope needs of the Nation. It will be important to maintain (and enhance as opportunities arise) the continuous dialogue with interested federal agencies, international suppliers, and commercial isotope customers to forecast and match realistic isotope demand and achievable production capabilities.

Transportation: With the establishment of the Transportation Working Group in the NIDC, the Isotope Program can continue to work toward improvements in the ability to safely and efficiently transport radioactive isotopes both nationally and internationally. Increasing regulatory demands and the use of a broad isotope production network will require increased collaborative efforts to resolve the priority issues in this area (i.e., standardized packaging and certified casks, consistent standards for both packaging and receipt of material). Due to the increasing rigor associated with all things related to security and safety, just keeping ahead of transportation issues will require special attention. In addition, the need for lower cost, higher availability, certified packaging is an immediate need.

Workforce Development: Investments in workforce development to educate and train the next generation of nuclear scientists focused on isotope production should continue to be a priority. Funding university programs at the undergraduate, graduate and postgraduate levels enable a highly trained workforce and can also generate new technologies and ideas. Support for junior faculty research funding through programs such as the DOE Early Career Awards enhances the prospects for permanent faculty engaged in isotope research (and the subsequent involvement of students). Finally, in response to the decline in undergraduate educational opportunities in the field of nuclear and radiochemistry and concomitant lack of student exposure to the field, the Isotope Program is encouraged to work closely with other DOE-SC programs to expose outstanding undergraduate science and engineering majors to nuclear science and radiochemistry.

Public/private partnerships: The 2009 NSACI recommendation for a dedicated accelerator for isotope production has been addressed by cost-effective development of additional capabilities at university production sites, and a Funding Opportunity Announcement (FOA) soliciting proposals on "Leveraging Isotope Program Resources and Enhancing Facilities" (including public/private partnerships). This is an appropriate response given budget constraints and the rapidly evolving commercial capability landscape. Development of these partnerships should continue and be assessed periodically.

Foreign supply: The Isotope Program has been identifying and keeping a list of critical isotopes for which the primary supply is from foreign sources and developing mitigation strategies in

cases of constrained supply. It should continue to update this list regularly. While these isotopes are not currently in short supply (and hence not directly part of the Isotope Program mission), for isotopes that are supplied in part or in whole by a foreign organization the Isotope Program is encouraged to continue to develop mitigation strategies, as appropriate, to minimize supply constraints and disruptions.

Strategic planning: Strategic planning for developing isotopes for commercial sales will continue to be a priority for the Isotope Program to maintain viability of the program. As commercial vendors start producing and selling isotopes that are now a major part of the DOE sales portfolio (e.g., ^{82}Sr), continuing assessments will be needed to judge how this will affect the long-term business of the Isotope Program. The research component of the Isotope Program will be of critical importance for developing the eventual successor to ^{82}Sr as the major sales item. Communication with users and strategic planning for the future will continue to be important for long-term viability of the program. The effort to form a network of university facilities that work with the isotope program is commended and should be continued. This, together with the goal of further enhancing workforce development, is the motivation behind our fourth major recommendation.

Chapter 10: Budget Scenarios

The charge to this subcommittee requests that "the plan should indicate what resources would be needed in the timeframe 2016-2025 to increase the domestic availability of isotopes appropriate to the DOE Isotope Program portfolio and deemed to be critical for the Nation". The proceeding chapters have made the case that while the DOE Isotope Program is functioning extremely well, the present level of appropriation carries with it considerable risk for the reliable availability of critical isotopes, and it is not adequate to allow the program to develop capabilities needed to respond to changing, future demand. Overall, within the current base appropriation funding, the program is exceptionally well run and extremely cost effective. These current activities must be continued for the program to remain healthy. Additional funds are needed to augment this effort so that the domestic supply of critical isotopes can be increased. The current shortfall is in four main areas: insufficient funds to carry out the highest priority R&D, insufficient resources to operate a new stable isotope production program, insufficient funds to build the necessary infrastructure critical to providing key isotopes, and lack of resources to broaden the base of production capability by leveraging expertise and facilities at the nation's universities.

The budget projections presented in this chapter are based on historical data for the period since the last NSAC Isotope Long Range Plan and the President's FY2015 request of 19.85 M$. The projections assume a continued constant level of effort at this value, quoted in FY2015 dollars, augmented by enhancements to the base appropriations needed to address the four recommendations of this report. Not included in this evaluation is the approximately 1M$ per year in SBIR funding, which is provided through the NP appropriation; the amount of funding from this source varies widely, from 100 k$ in FY2010 to 2.15 M$ in FY2013. Typically these grants enhance the commercial sale of isotopes by private industry and do not directly address the needs of the DOE Isotope Program. We assume that Isotope Program sales continue at the FY2014 level and that the fraction of sales revenue devoted to R&D and infrastructure maintenance remains at current levels. The conclusions of this chapter do not depend heavily on the volume of sales as income from sales is made on a cost-recovery basis and an increase or decrease in sales would result in proportional increases or decreases in the associated activities. However, the fractional expenditures for activities such as R&D should consider the size of the entire budget because appropriations would pay a proportionally higher share of activities that would address future supply.

Additional funding above the FY2015 appropriations will be required to increase isotope production. The first recommendation is to raise R&D funding to the level appropriate for an optimized healthy program. Research and development is central to the mission of the program to ensure an adequate supply of critical isotopes, allows the program to prepare for anticipated future demand, and provides the ability to deliver research quantities of novel isotopes that will likely lead to future breakthroughs. Enhanced R&D can be expected to increase the return on investment in the program as a whole. The history of the demand for ^{82}Sr (see Sidebar 11) illustrates the role of R&D. R&D was central to the development of the tools that allowed the program to increase supply towards meeting current demand, which in turn has led to increased demand; and to assist industry in increasing their production of this isotope. The current R&D program will lay the ground work for producing the next major isotopes, which are likely in the areas of alpha-emitters for therapy and theranostic isotope pairs. R&D is also necessary to explore new accelerator technologies, such as electron linacs, and advances in production targets.

An adequate R&D effort at each of the production sites is necessary for the program, yet the current level of funding does not allow this. At the current level of R&D funding, only about half of the highly rated proposals submitted to the competitive R&D FOA can be funded. The R&D FOA is currently issued once every two years due to constrained funding. The FOA should be issued every year and funds be added to allow the top rated proposals to be funded. Based on these considerations it is our judgment that the optimum budget would allocate an additional $4M per year in annual appropriations for R&D.

A critical need for the U.S. is to have in place a program that can produce high-enrichment stable isotopes. The DOE Isotope Program has relied on old stockpiles for inventory. Based on a recommendation from the last NSACI LRP a new stable isotope separation capability is being established. Additional base funds are needed to establish an operational program and to support operations of this new capability. In addition, investments will be necessary to improve the efficiency of isotope separators through development of new ion sources and improved materials chemistry. A reasonable goal that would match the critical part of the demand for U.S. stable isotopes should be to increase the throughput of the existing separator to be equivalent to at least that of one calutron (100 mA ion current). The addition to the base appropriations to operate a stable isotope production program is $2M per year.

The preceding chapters discussed the additional infrastructure needs of the program. The need includes funds to implement the harvesting of unused isotopes at FRIB. The future demand for certain alpha-emitters and theranostic pairs with high specific activity will require the development of an isotope separation capability for radioactive isotopes. Finally, there is a tremendous opportunity to enhance the production capability of the Isotope Program facilities by an intensity upgrade of the BNL BLIP accelerators and implementing a second target station; and by intensity, stability and energy upgrades at the LANL IPF. These latter improvements will be important for realizing the tremendous potential of targeted alpha therapy isotopes. The subcommittee estimates that the appropriate overall level of infrastructure investments of at least 25% of the program effort. This will require an increase in base appropriations of approximately $13.5M per year for the period covered by this Long Range Plan. *Considering the infrastructure investment levels since the 2009 NSACI reports, the identified needs for the immediate future, and the anticipated needs for the longer-term, this level of infrastructure support should become part of the base budget for IDPRA if they are to develop and maintain the domestic availability of isotopes appropriate to the DOE Isotope Program portfolio and deemed to be critical to the nation.* Cost details for the period covered by this Long Range Plan are provided in Figure 18 and Figure 19 and the following paragraphs.

The fourth area of need is funds to allow the DOE Isotope Program to leverage the facilities and skilled workforce that exists at the U.S. university facilities. University facilities have the ability to cost-effectively augment the capabilities of the national laboratories, and to meet demands for radioisotopes and radioisotope R&D that are not possible at the national laboratories, such as regional production of short-lived radioisotopes (e.g. ^{211}At) and evaluation of some alternative methods for radioisotope production. Partnership with university sites can also provide complementary and/or supplemental capabilities for production of isotopes. Funds will be necessary for facility improvements at the university labs to allow them to enhance production of critical isotopes. Investments for facility improvements at the universities investments would be cost effective and use approximately $1M of the $13.5M/year increase in infrastructure funding

that we are recommending. These investments will have the additional benefit of strengthening the pipeline for a trained workforce for the future.

The budget implications and time sequence of these activities are illustrated in Figure 18 and Figure 19. The figures show how the funds for the current program have been allocated, in FY2015 dollars. Historical and projected funding of operations, R&D, and facility maintenance and improvements are included. The level of effort assumed for FY2015 in the base budget is carried into the out years. Starting in FY2017 the graph includes increases for the initiatives that would be needed to increase production of critical isotopes. The additional R&D includes $2M for raising the base R&D at the production facilities and $2M to fund high priority R&D that is now unfunded. An additional $2M is projected to operate the stable isotope production program. The ongoing initiatives to strengthen the capabilities of the university facilities in the field would be funded at $1M per year (as part of the $13.5M/year infrastructure funding increase we are recommending), and should be determined by competitive peer review.

The proposed facility infrastructure investments for the period covered by this Long Range Plan can be time sequenced so that the sum is roughly constant. The ordering we have used in assembling the budget profile reflects practical realities of the readiness of the projects along with implications of delays rather than simply reflecting their scientific priority. Early in the period a sum of $9M is included for infrastructure for harvesting of isotopes at FRIB. This is time critical as ideally these investments should be made prior to the start of operations at FRIB to minimize disruptions to the facility's scientific program; they should be initiated soon after a feasibility review of the plans. Also early in the period would be the LANL IPF diagnostic improvements to enhance beam power and stability ($5.5M). The LANL IPF energy upgrades would start in FY2017 ($10M). Intensity upgrades at BNL BLIP (~$8M) would begin early, followed by the implementation of a second target station at BNL BLIP (~$18M). Funds are included throughout the period for the build-up of parents of alpha emitters at ORNL(~$2M per year starting in FY2018, $15M total). The subcommittee did not have an estimated cost for the radioisotope separator, and assumed that this was a longer term item with a cost of approximately $20M, with spending starting once the FRIB harvesting project was mostly completed. That would place funding for its construction after the period covered by this Long Range Plan.

Figure 19 provides the same information but broken down by funding category. The same initiatives are included to illustrate their relative size to the base budget. All values given in the figure are in FY2015 dollars. The needed funding increments to increase production of critical isotopes to match the anticipated demand would raise the appropriations level to approximately what was available in FY2009 with the addition of ARRA funds. The ARRA funds were critical to stabilize the program and allow it to meet the current demand. The additions we recommend to R&D would bring the fractional spending in this area close to 15%. Infrastructure spending would allow the areas of most significant need to be addressed and the total spending on infrastructure would be close to 25% of total spending.

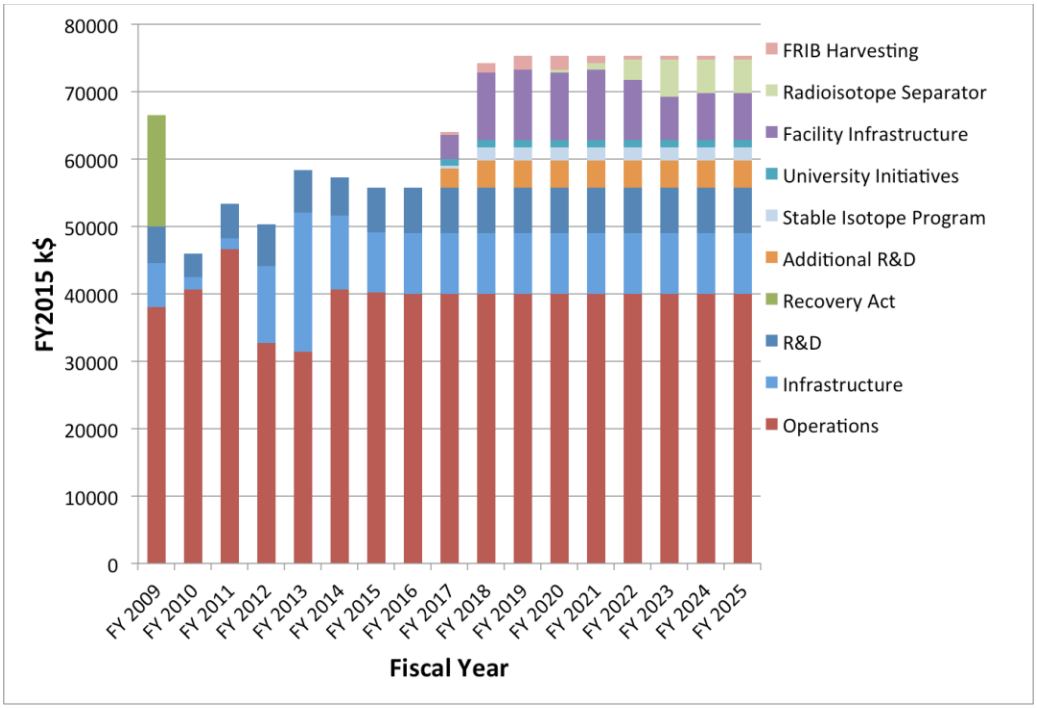

Figure 18: Historical and projected DOE Isotope Program funding by category in FY2015 k$. The total values include both base appropriations funding and funding from sales.

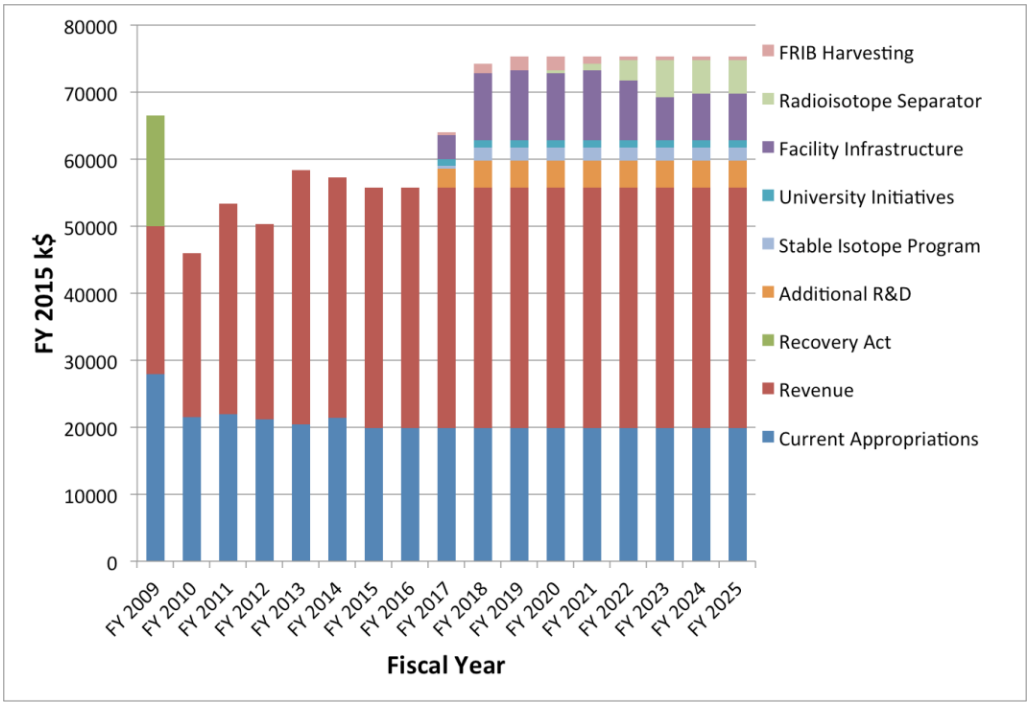

Figure 19: Historical and projected DOE Isotope Program funding by funding category in FY2015 k$. The new initiatives discussed in the report are included. The total values include both base appropriations funding and funding from sales.

In summary, the funding increases outlined here will position the DOE Isotope Program to prepare for the projected increase in demand of alpha-emitters for therapy and theranostics for personalized medicine as a major current focus of the program, ^{82}Sr, transitions to commercial suppliers. The funding will also reestablish the regular production of stable isotopes, removing the dependence of the U.S. on foreign sources. It will allow the program to take advantage of opportunities to harvest isotopes at FRIB that are in short supply or have no source. The increases will allow the program to leverage unique facilities and personnel at the U.S. university facilities to both meet isotope demand, but also to assist in ensuring a qualified isotope workforce in the future. While the current program is cost effective and well managed, it has become clear that an optimal program requires an increase in the base support supplied by appropriations.

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Appendices:

Appendix 1: The NSAC Charge to NSACI

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Argonne National Laboratory
9700 South Cass Avenue, Bldg. 203
Argonne, IL 60439-4845

Argonne NATIONAL LABORATORY

October 30, 2014

Dr. Lawrence Cardman
Jefferson Lab
12000 Jefferson Ave Ste. 6
Newport News, VA 23606-4468

Dear Larry,

As you know Patricia Dehmer, Acting Director of the Office of Science at the Department of Energy, and F. Fleming Crim, Assistant Director of Math and Physical Sciences of the National Science Foundation, have charged NSAC to form an Isotope Subcommittee to conduct a new study of the opportunities and priorities for isotope research and production. This effort should result in a long range strategic plan for the Department of Energy Isotope Program that is managed by the Office of Science for Nuclear Physics. The charge is attached.

I am writing to formally ask you to serve as the Chair of the NSAC Subcommittee to consider this charge and report back to NSAC. The Subcommittee will be a standing Subcommittee for an initial period of two years. The charge requests an interim report containing the essential components of the recommendations followed by a final report by March 2015. To allow NSAC time to consider your report, I must ask your subcommittee to submit its report to NSAC by March 15, 2015.

The report should articulate the scope and scientific technical challenges of isotope research and production, document the progress since the last NSACI sub-committee published its recommendations, and identify and prioritize the most compelling opportunities for the DOE Isotope Program to pursue over the next decade. It should also indicate what resources would be needed in the time frame 2016-2025 to increase the domestic availability of isotopes appropriate to the DOE Isotope Program and deemed critical for the Nation. Stakeholder communications are an important element in your charge as well as the effectiveness of the program in the provision of critical isotopes.

I realize this is a heavy responsibility. I, and our whole community, will owe you an enormous debt of gratitude.

Sincerely yours,

Donald F. Geesaman
Chair, NSAC

U.S. Department of Energy
and the
National Science Foundation

April 23, 2014

Dr. Donald Geesaman
Chair
DOE/NSF Nuclear Science Advisory Committee
Argonne National Laboratory
9800 South Cass Avenue
Argonne, Illinois 60439

Dear Dr. Geesaman:

This letter is to request that the Nuclear Science Advisory Committee (NSAC) establish an NSAC Isotope (NSACI) sub-committee to conduct a new study of the opportunities and priorities for isotope research and production. This effort should result in a long range strategic plan for the Department of Energy (DOE) Isotope Program, managed by the Office of Science for Nuclear Physics. It is envisioned that NSACI will be constituted for a period of two years.

Stable and radioactive isotopes continue to play a critical role in enabling many basic research and applied programs in medicine, industry, and national security. They are vital to the mission of many Federal agencies. The new study by NSACI should articulate the scope and the scientific/technical challenges of isotope research and production today, what progress has been made since the last NSACI sub-committee published its recommendations, and the scientific and societal impacts of these accomplishments and ongoing activities. It should identify and prioritize the most compelling opportunities for the DOE Isotope Program to pursue over the next decade and articulate their impacts.

To be most helpful, the plan should indicate what resources would be needed in the timeframe 2016-2025 to increase the domestic availability of isotopes appropriate to the DOE Isotope Program portfolio and deemed to be critical for the Nation. Important aspects of this assessment should consider: existing technical capabilities and infrastructure, the robustness of current isotope production operations, research and development of production techniques for research and applied isotopes, production of research isotopes, and development of core competencies. As you know, the Isotope Program provides the facilities and capabilities for the production of research and commercial stable and radioactive isotopes only where there is no U.S. private sector capability or when other production capacity is insufficient to meet U.S. needs.

The plan should also consider other aspects of the DOE Isotope Program that are relevant and important to stakeholder communications and the effectiveness in the provision of critical isotopes to the Nation.

We request that you submit an interim report containing the essential components of NSACI's recommendation to the DOE, followed by a final report by March 2015. We appreciate NSAC's willingness to take on this vitally important task, and look forward to receiving its report.

Sincerely,

Patricia M. Dehmer
Acting Director
Office of Science

F. Fleming Crim
Assistant Director
Directorate for Mathematical
and Physical Sciences

Appendix 2: Membership of NSAC Isotope Subcommittee

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[1] David A. Scheinberg is an inventor of alpha particle technology discussed in this report and is a paid consultant to a company that has licensed the technology.

NSACI Subcommittee Meeting I, September 23, 2014

9:00	Welcome	Larry Cardman
9:10	Charge from NSAC Chair	Don Geesaman
9:20	Introduction	Larry Cardman
9:45	The DOE Isotope Program Today: Overview and Perspective	Jehanne Gillo
11:15	Coffee Break	
11:30	Isotope R&D	Dennis Phillips
12:10	Lunch	
1:10	Stable and Accountable Materials	Joel Grimm
1:40	Isotope Production Facilities and the National Isotope Development Center	Marc Garland
2:25	Isotope Business Office Operations	Mitch Ferren
2:55	Customer Interactions and Demand Forecast	Wolfgang Runde
3:25	Coffee Break	
	Sample Perspectives of Isotope Users – Agencies	
4:25	NIH as a major customer	Tony Sastre
5:00	Discussion of the Charge and the path forward	
6:00	Adjourn	

NSACI Subcommittee Meeting II, November 20-21, 2014

November 20, Morning: Agency Needs and Issues

9:00	Welcome, Summary of Information Received, and Overview of the Plan for the Meeting	Larry Cardman
9:30	NIST	Scott Dewey
9:50	DHS and the National Technical Forensic Center	Richard Essex (NBL)
10:10	DOE Office of Nuclear Energy	Richard Reister
10:30	Coffee Break	
10:45	DOE Office of Fusion Energy	Gene Nardella
11:05	DOE Office of Basic Energy Sciences: input from BES users (3 written, 1 presentation)	Lynda Soderholm (ANL)
11:25	NNSA	Joel Smith
11:45	NSF	Allena Opper
12:05	Lunch	
1:00	Oil and Gas Exploration	Frank Yeager
1:20	Radiopharmaceuticals (Council of Radionuclides and Radiopharmaceuticals)	Michael Guastella
1:50	Association of Energy Service Companies	Eric Rosemann
2:10	Zevacor - 70MeV cyclotrons and commercialization of 82Sr	John Zehner
2:30	Industrial Producers – SPEC	Dennis Chedraui
2:50	Braco - supplies 82Sr and gets their supply from multiple sources including DOE	Adrian Nunn
3:10	Coffee Break	
3:30	Introduction to ^{99}Mo discussion: NNSA vs NP and special ^{99}Mo subcommittee vs NSACI	Don Geesaman
3:40	NSAC ^{99}Mo Subcommittee Review/Findings	Tom Ruth
4:40	General discussion of plans for Meeting III	
5:00	Adjourn	

November 21st Completion of Presentations on Agency and Industry Needs and Issues, then an Executive Session to Begin Planning for and Discussion of the Content of our Report

9:00	General Summary of plans for the day and for Meeting III (January 20-21)	Larry Cardman
	Begin with presentations that would have been yesterday, but were delayed due to schedule conflicts	
9:10	DOE Office of Nuclear Energy – Office of Space and Defense Power Systems	Rebecca Onuschak
9:30	DoD	Craig Wuest
9:50	DOE/NP	Tim Hallman
10:10	Coffee Break	
	Executive Session for the remainder of the day (closed to the public)	
10:30	General Discussion of Process, and a Summary of written input received to date from Agencies and Industry for those who are not making a presentation	L. Cardman
11:00	Discussion (for the remainder of the day) chapter by chapter of the plans for writing the report and the current status of ideas for recommendations and evaluation comments	All
5:30	Adjourn	

NSACI Subcommittee Meeting III, January 20-21, 2014

January 20: Professional Societies, then University and DOE Laboratories

9:00	Introduction to the day	Lawrence Cardman
9:15	TRTR (The National Organization of Test, Research, and Training Reactors)	Ralph Butler
9:35	ACS/DNCT (American Chemical Society / Division of Nuclear Chemistry and Technology)	Paul Mantica
9:55	SNM (The Society of Nuclear Medicine)	Erin Grady
10:15	Coffee Break	
10:30	Isotope Production at TRIUMF	Jonathan Bagger
	University Sites – status and plans (A series of brief presentations)	
10:45	University of Washington	Scott Wilbur
11:00	Washington University	Suzanne Lapi
11:15	MURR	David Robertson
11:30	University of Wisconsin	Jerry Nickles
11:45	Summary of other University sites (Duke, Texas A&M, UC Davis).	Scott Wilbur
12:00	Working Lunch (Discussion of Issues and Budgets for the University Sites)	Scott Wilbur and Suzanne Lapi
1:00	ORNL (General)	John Krueger
1:40	INL	Debbie Utterbeck
2:05	NSCL	Dave Morrissey
2:30	BNL	Leonard Mausner
2:55	LANL	Eva Birnbaum
3:20	Coffee	
3:35	SRNL	Jeff Allender
4:00	PNNL	Gertrude Patello
4:25	Discussion of Production Site budget issues	Brad Sherrill, Lee Riedinger
5:30	Adjourn	

January 21st: Executive Session all day to Complete Planning for and Discussion of the Content of our Report and, in particular, the Development of our Recommendations and Evaluation

Appendix 4: List of Federal Agencies Contacted by NSACI

Army Research Lab
Air Force Office of Scientific Research
Armed Forces Radiobiology Research Institute
Bureau of Land Management (BLM)
Defense Logistics Agency
Defense Threat Reduction Agency
DoD
Department of Agriculture
DOE/National Nuclear Security Administration
DOE Office of Basic Energy Sciences
DOE Office of Biological and Environmental Research
DOE/Office of Fossil Energy-Oil and Natural Gas
DOE Office of Fusion Energy
DOE Office of High Energy Physics
DOE/Office of Intelligence
DOE Office of Nuclear Energy
DOE Office of Nuclear Energy, Office of Space and Defense Power Systems
DOE Office of Nuclear Physics
Department of Homeland Security
Department of Homeland Security - National Technical Nuclear Forensics Center
Department of State
Department of Transportation
Federal Bureau of Investigation / DHS / National Technical Forensics Center
Food and Drug Administration
National Aeronautics and Space Administration
National Institutes of Health
(National Institute of Biomedical Imaging and Bioengineering to cover for all of NIH)
National Institute of Standards and Technology
National Science Foundation Directorate for Mathematical and Physical Sciences
Office of the Director of National Intelligence
Office of Naval Research
U. S. Geologic Survey

Appendix 5: List of Professional Societies Contacted by NSACI

Academy of Radiology Research
American Association of Physicists in Medicine
American Association of Cancer Research
American Chemical Society
American Chemical Society - Division of Nuclear Chemistry and Technology
American College of Nuclear Physicians
American College of Radiology
American Medical Association
American Nuclear Society
American Nuclear Society - Division of Isotopes and Radiation
American Pharmacists Association - Academy of Pharmaceutical Research and Science (APhA-APRS)
American Physical Society - Division of Biological Physics
American Physical Society - Division of Material Physics
American Physical Society - Division of Nuclear Physics
American Society of Clinical Oncology
American Society of Hematology
American Society of Nuclear Cardiology
American Society of Therapeutic Radiation and Oncology
Council on Ionizing Radiation and Standards
Health Physics Society
National Association of Nuclear Pharmacies (NANP)
National Organization of Test, Research and Training Reactors
Radiation Research Society
Radiation Therapy Oncology Group
Radiological Society of North America
Society of Nuclear Medicine
Society of Radiopharmaceutical Sciences (SRS)
United Pharmacy Partners (UPPI)

Appendix 6: List of Industry and Trade Groups Contacted by NSACI

Association of Energy Service Companies
ARRONAX, Nantes, France
Braco
Cambridge Isotopes
Eckert & Ziegler Vitalea Science (Oil and Gas Exploration)
EPRI (The Energy Power Research Institute)
GE Healthcare,
Jubilant Draximage
Linde
Mallinckrodt (Radiopharmaceuticals)
Perkin Elmer
Radiopharmaceuticals (Council of Radionuclides and Radiopharmaceuticals)
Source Production & Equipment Co., Inc (SPEC)
Trace Sciences
Zevacor

Appendix 7: Details about Isotope Stockpiles and the Isotopes Available from them.

In this appendix we provide some details about the history and disposition of the isotope stockpiles summarized in Section 6.D of our report and listed in Table 13 there, along with further information on the isotopes available from these stockpiles and their uses, as listed in Table 14 of Section 6.D.

Isotope Stockpiles

SRS MK-18A (^{242}Pu) and MK-42 (^{239}Pu) Irradiated Targets.

The SRS MK-18A consists of ^{242}Pu targets irradiated in K-Reactor for up to 10 years. The primary mission was to produce the world's first multi-gram quantities of ^{252}Cf. During the 10-year irradiation the targets were exposed to the highest thermal neutron fluxes ever produced in a nuclear reactor. Twenty-one of the MK-18A targets were processed at ORNL in the 1970s to provide californium and most of the world's supply of ^{244}Pu and heavy curium, but these supplies are depleted.

Sixty-five additional MK-18A targets remain in storage at the Savannah River Site (SRS). The NNSA Office of Nuclear Materials Integration (OMNI) is sponsoring a program to process some or all of the remaining targets and make available the unique isotopes that are impossible to recreate with existing U.S. facilities. They have established an interagency working group to coordinate interest and distribution of materials from the processing of the targets; the DOE Isotope Program is represented on this working group and has expressed interest in supporting the processing of certain isotopes in the MK-18 targets. The ^{244}Pu is in high demand for high-precision plutonium measurements because it is not created by any other source, and the curium that now contains more than 80% of heavy curium isotopes, $^{245\text{-}248}$Cm, is the most attractive feed available for the production of new transcurium isotopes.

The MK-42 consists of ^{239}Pu targets irradiated in the C-Reactor at SRS for 3-4 years, primarily to produce ^{242}Pu (for NNSA Defense Programs), ^{243}Am, and ^{244}Cm. Most of MK-42 targets have been processed for use by existing DOE programs. Processing of MK-42 targets, was suspended when inventory of ^{242}Pu reached an adequate level, consequently, 28 unprocessed target segments and 104 capsules of processed Am-Cm-fission product remain in inventory at ORNL as of FY 2011. The Am-Cm oxides are a potential supply of high-isotopic purity ^{240}Pu but the Am and Cm fraction of the MK-42 materials is considered much less attractive for use in future heavy isotope production than the heavier actinide fraction of the MK-18A targets because of ^{241}Am content However, each MK-42 target also contained ~2.7 kg of fission products. Thirty Am-Cm capsules were processed in FY2011-FY2013 and 1 kg of Ln fission products were removed (and disposed of as waste) to make it more attractive for heavy isotope production. The fission products removed were disposed of as waste. If retained this fission product inventory contained multi-milligram to multi-gram quantities of very long-lived fission products of interest, including ^{79}Se, ^{93}Zr, ^{99}Tc, ^{107}Pd, ^{126}Sn, ^{129}I, ^{139}La, and many other light lanthanides. The isotopic distributions of these fission product isotopes (produced by fission of ^{239}Pu) are far more attractive than what can be produced by direct transmutation of the lighter stable isotope

precursors. The production and destruction of these isotopes in a nuclear reactor (neutron cross section studies) and their subsequent impact on waste disposal are of interest. ^{93}Zr has been recovered in multi-gram quantities during a campaign at the ORNL.

A summary of the isotope inventory in MK18A and MK42 is given in Table 16. The present inventory of MK-42 materials at ORNL REDC that require disposition is given in Table 17.

Table 16: MK-42 and MK-18A Inventory Summary FY 2011

Item	Location	Pu (grams)	^{241}Am (grams)	^{243}Am (grams)	^{244}Cm (grams)	^{245}Cm (grams)	^{246}Cm (grams)	^{248}Cm (grams)
Mk-42 (28 Unprocessed Target Segments)	ORNL	1164	113	182	60.8 (84.5%)	5.1 (7.1%)	5.6 (7.8%)	0.3 (0.4%)
Mk-42 (104 Am/Cm/Ln Oxide Capsules)	ORNL	79	76	409	151.8 (80.3%)	12 (6.3%)	22,8 (12.1%)	1.7 (0.9%)
Mk-18A (65 unprocessed assemblies)	SRS	400	15	19	133,3 (19.7%)	9.9 (1.45%)	471,3 (69.6%)	44.05 (6.5%)

Decayed to 10/01/2011

Table 17: Present Inventory of MK-42 Materials at ORNL REDC that Require Disposition

Item	Am (grams)	Cm (grams)
28 Unprocessed Target Segments	295	72
74 Am/Cm/Ln Oxides Capsules	386	147
6 Purified Am/Cm Capsules	98	42
Total	779	261

Uranium-233 ^{233}U was produced in Savannah River and Hanford Reactors, most efficiently via neutron capture of ^{232}Th. A portion of the irradiated fuel was processed at ORNL. The ^{233}U material at ORNL has been separated from fission products and contains only ^{229}Th (the α-decay daughter of ^{233}U) and ppm levels of ^{232}U and Pu isotopes and their decay daughters. Some ^{233}U also remains at INL in the form of two UO_2-ThO_2 cores for the Shipping Port LWBR test. One core is un-irradiated and the other was irradiated. ^{233}U can be also be produced at a much smaller scale via the α-decay of ^{237}Np followed by β^--decay of 27-d ^{233}Pa. ^{233}U has a variety of applications and research interests. The most visible and important application of ^{233}U is as a "cow" for the production of ^{229}Th the current primary source for the production ^{225}Ac for medical applications which was discussed in some details in section 3A. In 2013, the DOE Isotope Program accepted 125g of ^{233}U that had been identified as high purity material by the

NNSA during the course of the disposition planning of the ORNL stockpile. The remainder of the high purity material was distributed to other agency organizations for various applications. A small amount of this Isotope Program material will be provided for the development of certified reference materials; the majority will be used as a "cow" for medical purposes.

Plutonium-244 ^{244}Pu- is the longest-lived Pu isotope, ($t_{½} = 8.0 \times 10^7$ y). ^{244}Pu is not present in reactor-produced Pu or weapons-grade Pu. This lack of ^{244}Pu in all other existing Pu stock makes it the perfect radio-tracer; it is particularly critical to detection of Pu in environmental samples, forensic studies including the accurate measurement of declared reactor fluxes. Its very long half-life and heavy mass make it a valuable target material for the production of super-heavy elements and allows for bench-top experiments with Pu for a better understanding of the fundamental chemistry of Pu. The world's supply (~3 grams) of separated and enriched ^{244}Pu originated from the processing of 21 of the MK-18A targets (discussed above) followed by and enrichment by Calutrons at ORNL. Another ~20 grams of unprocessed and un-enriched ^{244}Pu remain in the irradiated MK-18A targets. This is the world's inventory of ^{244}Pu. It will not be produced again in these quantities.

Americium-243 The ^{243}Am (with ~70 atom %) inventories in MK-18A and 42 (see above) represents essentially the entire inventory of ^{243}Am in the United States with the exception of several grams scattered throughout the DOE complex. Inventory amounts are on the order of hundreds of grams. Potential uses of the ^{243}Am are as feedstock to future actinide enrichment devices, source material for minor actinide transmutation studies and experiments and as target material for the production of trans-americium elements. The DOE Isotope Program has access to these inventories of ^{243}Am and this isotope is available for distribution.

Americium-241 in Excess of NNSA stockpiles The planned primary inventory site for ^{241}Am is Los Alamos National Laboratory (LANL). Am-241 is produced through the β^--decay of ^{241}Pu ($t_{1/2}$ = 14.29 yrs), which is produced by irradiations of U and Pu targets in a nuclear reactor. Although, the ^{241}Am is diluted by the presence of ^{243}Am, it can be produced essentially isotopically pure from the decay of separated Pu. The DOE complex has a significant inventory of excess Pu and NNSA Pu is a potential source of ^{241}Am. Currently, there is no large inventory of separated ^{241}Am remaining in the United States and the last batch was sold to foreign customers. ^{241}Am has a multitude of uses. It is used extensively in well logging by the oil and gas industry and widely used in smoke detectors. At present, there is only one foreign supplier. In 2011, the DOE Isotope Program, in concert with an industrial consortium, initiated a project at LANL to reestablish their ^{241}Am production capability. Product is expected to become available starting in 2017.

Isotopes Available from the Stockpiles

Here we provide further information on the isotopes available from the stockpiles (summarized in Table 14 of Section 6.D of our report) and a brief description of some of their uses.

Heavy and Light Cm In the transmutation route for the production of ^{252}Cf, the Cm isotopes, ^{244}Cm through ^{248}Cm, are produced. Due to the long irradiation time and long out-of-reactor decay of the MK-18A targets, the Cm isotopic distribution has become heavier. This "heavy"

Cm isotopic distribution makes the Cm excellent target material for the production of the transcurium elements up to Fm.). In addition to the production of transcurium elements, the heavy Cm is a potential feedstock for the actinide enrichment of $^{246, 247, 248}$Cm. Enriched ^{247}Cm would be ideal for radiochemistry and solid state actinide chemistry because of its long half-life. Light Cm, Cm enriched in ^{244}Cm, was produced in multi-gram amounts with inventories of 200 grams. This inventory, along with some other SRS-produced Cm, essentially represents the total inventory of light Cm in the United States. The light Cm is suitable target material for the production of transcurium elements (the yield is lower than that for heavy Cm). Several years of irradiation in the ORNL HFIR could transmute it to heavy Cm which is an optimum target material for heavy element production; in fact, this is an approach that is employed by the DOE Isotope Program for ^{252}Cf production. In addition to the production of transcurium elements, the light Cm is a potential feedstock for the actinide enrichment of ^{244}Cm and ^{245}Cm and source material for specific RTGs.

Thorium-229 Figure 20 below depicts one of ORNL's most celebrated "trash to treasure" projects which is entering its 116th campaign of ^{229}Th and ^{225}Ac processing. The ultimate source of this medical radioisotope is ^{233}U (Figure 21). Since starting in 1995, ORNL researchers have developed and refined a process to transform surplus ^{233}U through a chain of daughter isotopes – ^{229}Th to ^{225}Ac, which is shipped to clinics. Since 1997, ORNL has been the main supplier of high purity ^{225}Ac from decay of existing ^{229}Th stock and, to date, ORNL has made over 700 shipments to external customers (totaling 7.9 Ci of ^{225}Ac) through the Isotope Program. Since 2011, ~720 mCi of ^{225}Ac is harvested annually from the ^{229}Th stock, typically in six campaigns per year. It would be possible to increase the annual yield by another 20% by increasing the number of campaigns per year. The approach, however, will result in an increase in unit cost ($/mCi).

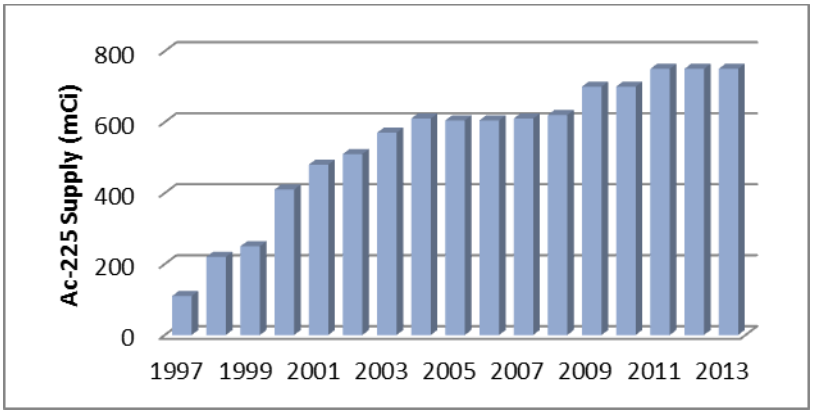

Figure 20: ^{225}Ac production capacity (mCi) at ORNL from decay of ^{229}Th

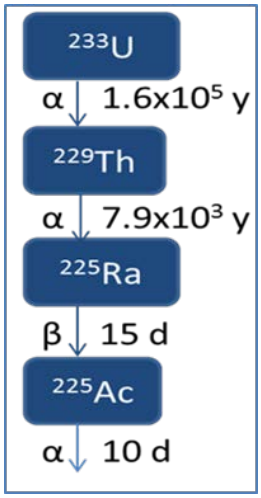

Figure 21: The ^{233}U decay scheme

Actinium-227 The DOE Isotope Program supported the recovery of ^{227}Ac from ^{227}AcBe sources at ORNL in order to provide the medical community with high purity alpha emitters ^{227}Th and ^{223}Ra. ^{227}Ac is also a potential reactor target for the production of ^{229}Th parent of alpha-emitters

^{225}Ac, and ^{213}Bi. A total of 500 mCi of ^{227}Ac was is currently in storage at ORNL and a similar amount is available from PNNL.

Thorium-228 ^{228}Th is the second member of the ^{232}Th decay chain and it is also the α-decay product of ^{232}U. ^{228}Ra ($t_{1/2}$ = 5.8 y) can be extracted from ^{232}Th, purified, then allowed to decay to ^{228}Th. Each ton of 30-year old ^{232}Th yields ~100 mCi of ^{228}Ra. ^{228}Th, however, can be produced from successive neutron capture and ß$^{-}$ decay of ^{226}Ra . This irradiation has been demonstrated in the past to be feasible. A small stock of ^{232}U and somewhat large amount currently exists at ORNL and PNNL, respectively. ^{224}Ra separated from ^{228}Th, adsorbed on an organic cation exchange resin, provides a convenient means for in situ production of short-lived ^{212}Pb and ^{212}Bi for use in targeted alpha therapy. Up to 20 mCi ^{224}Ra generators are currently available through the DOE Isotope Program.

Neptonium-237 ^{237}Np does not occur in nature; however, it is produced in civilian and defense nuclear power reactors. Commercial reprocessing programs aimed at plutonium and uranium recovery have not separated significant amounts of neptunium, and majority of the ^{237}Np remains contained either in the spent fuel or in the process waste. The bulk of the U.S. military Np was produced in the Pu and ^{3}H production reactors at the Savannah River site. A lesser amount was produced in the reactors at the Hanford reservation. All of these reactors are now shut down. Relatively small amount of Np has also been produced in naval reactor fuel.

The main application of ^{237}Np is as target for production of ^{238}Pu. Similarly, ^{238}Pu does not occur in nature, and unlike ^{239}Pu, it is unsuitable for use in nuclear weapons, and it has been primarily used in radioisotope thermoelectric generators (RTG), mainly in support of NASA space missions since the early days of Apollo program. RTGs still function on the lunar surface, and are on the farthest man-made object, Voyagers 1 and 2, now near 100 AU from Earth. No ^{238}Pu has been produced in the U.S. since the shutdown of the processing facilities in the late 1980s. Since then, the U.S. space program has had to rely on the existing inventory of ^{238}Pu, supplemented by the purchase of ^{238}Pu from Russia. However, Russian facilities to produce ^{238}Pu were also shut down many years ago. Consequently, the total amount of ^{238}Pu available for NASA is fixed, and essentially all of it is already dedicated to support several pending missions; the Mars Science Laboratory, Discovery 12, the Outer Planets Flagship 1 (OPF 1), and (perhaps) a small number of additional missions with a very small demand for ^{238}Pu. The DOE Office of Nuclear Energy (NE) is working with NASA to restart ^{238}Pu production for the specific purpose of RTG fabrication, which NE has historically fabricated for NASA. Thus, NE has the lead within the DOE on re-establishing ^{238}Pu production at HFIR; excess material would be available for distribution through the Isotope Program.

The ^{238}Pu production mechanism in a nuclear reactor involves neutron capture of ^{237}Np to ^{238}Np which decays with a half-life of 2.1 d to ^{238}Pu. The very large fission cross- section of ^{238}Np, 2600 b, however, limits the ^{238}Pu yield. The required amount of ^{237}Np target material ranges from kg to tens of kg, and most likely the Np target material has to be recycled. As a part of the preparation of the Np target, ^{233}Pa ($t_{1/2}$=27 d), the α-decay daughter of ^{237}Np, has to be removed, providing an opportunity for small but very high purity sources of ^{233}U.

Appendix 8: Stable Isotope Demand (NIDC 2011)

Table 18: Stable Isotope Demand [NIDC, 2011]

Note: This list is updated and prioritized periodically by NIDC – an update is currently underway. Note also that the quantities demanded have been omitted as from the table as they are business sensitive information in some cases for customers of the Isotope Program.

LIST OF STABLE ISOTOPES			
ISOTOPE	**PRIMARY METHOD OF ENRICHMENT**	**APPLICATION(S)**	**GENERAL COMMENTS**
^{3}He	Tritium decay product	- Neutron detectors for nuclear non-proliferation applications - Well logging in oil & gas industry. - Nuclear & condensed matter physics research. - He dilution refrigerators. - MRI lung imaging	
^{6}Li	Chemical exchange	- Basic constituent in neutron dosimeters. - Precursor for the reactor production of tritium. - Thermonuclear weapons.	Commercial market growth in neutron detectors. Research needs for ITER expected to be ~45,000 kilograms.
^{7}Li	Chemical exchange	- Used as an alkalizing addition to PWR coolant to regulate water chemistry.	Commercial market growth expected for development of AHTR. Fusion reactors are projected to require thousands of kilograms.
^{28}Si	Centrifuge	- Nuclear physics research (Avogadro Project)	Supplied by foreign source.
Ti (depleted in ^{46}Ti)	Centrifuge	- Used for radioactive medical seed encapsulation prior to irradiation. - The depletion of ^{46}Ti minimizes the production of ^{46}Sc which increases radiation levels to unacceptable levels.	Potential future use for irradiation capsule material in reactor produced radioisotopes.
^{62}Ni	EMIS, Centrifuge	- Precursor for reactor production of ^{63}Ni. - ^{63}Ni is used as the active source for explosive and drug detection systems at airports and other security/safety related venues. - ^{63}Ni is used in beta batteries for power.	Generally 25 grams needed for reactor targets every two to three year to produce 300 curies of ^{63}Ni.

LIST OF STABLE ISOTOPES			
ISOTOPE	**PRIMARY METHOD OF ENRICHMENT**	**APPLICATION(S)**	**GENERAL COMMENTS**
^{64}Ni	Centrifuge, EMIS	- Precursor for accelerator production of ^{64}Cu. - ^{64}Cu is a PET imaging agent for cancerous tumor imaging. - Radioimmunotherapy. - Study Cu retention in the body.	^{64}Cu is currently used in clinical trials. High enriched ^{64}Ni (>99%) is required. Foreign supplier will discontinue production on 2012.
Zn (depleted in ^{64}Zn)	Centrifuge	- Zn is used as a corrosion inhibitor in commercial nuclear power coolant. - The depletion of ^{64}Zn minimizes the production of ^{65}Zn which can elevate radiation levels in the coolant systems. - Oxide form used for BWRs and acetate form used for PWRs.	Foreign sources supply the commercial market.
^{68}Zn	Centrifuge, EMIS	- Precursor for cyclotron production of ^{67}Ga. - ^{67}Ga is used as an imaging agent to diagnose bone and joint infection, pulmonary lesions, and urinary tract infections.	Foreign sources supply the commercial market.
^{74}Se	Centrifuge	- Precursor for the production of ^{75}Se. - ^{75}Se is used as a gamma radiography source for NDT of welds in pipelines and shipbuilding.	Foreign sources supply the commercial market.
^{76}Ge	Centrifuge	- Nuclear physics research (Majorana Collaboration)	Supplied by foreign source.
^{87}Rb	EMIS	- Atomic frequency emission is ideal for high- precision communication systems such as global positioning &cell phone tower transmissions. - Used in atomic clocks. - Used in geochronology studies.	
^{88}Sr	EMIS	- Precursor for reactor production of ^{89}Sr. - ^{89}Sr is the active ingredient for Metastron™, the FDA-approved product to treat bone metastases in bone cancer patients.	Foreign sources supply the commercial market.

LIST OF STABLE ISOTOPES			
ISOTOPE	**PRIMARY METHOD OF ENRICHMENT**	**APPLICATION(S)**	**GENERAL COMMENTS**
^{98}Mo	Centrifuge, EMIS	- Precursor for reactor production of ^{99}Mo/^{99m}Tc. - ^{99m}Tc is used as the imaging agent for brain, heart, and renal scans. - Approximately 85% of diagnostic imaging in nuclear medicine uses ^{99m}Tc.	
^{100}Mo	Centrifuge, EMIS	- Precursor for accelerator production of ^{99}Mo/^{99m}Tc.	
^{112}Cd	Centrifuge, EMIS	- Precursor for cyclotron production of ^{111}In. - ^{111}In is an imaging agent for detection of prostate cancer and labeling blood components.	Foreign sources supply the commercial market.
^{130}Te	Centrifuge	- Nuclear physics research (Cryogenic Underground Observatory for Rare Events)	Supplied by foreign source.
^{176}Yb	EMIS	- - Precursor for indirect production of - ^{177}Lu. - - Multiple therapeutic applications where - shallow beta penetration (2.76 mm max) is - useful.	
^{176}Lu	EMIS	- Precursor for reactor production of ^{177}Lu. - Multiple therapeutic applications where shallow beta penetration (2.76 mm max) is useful.	
^{186}W	Centrifuge, EMIS	- Precursor for high flux reactor production of ^{118}W used in ^{188}Re generators - Multiple diagnostic and therapeutic applications.	
^{203}Tl	EMIS	- Precursor for cyclotron production of ^{201}Tl. - ^{201}Tl is used for heart imaging to determine damage from heart attacks.	Foreign sources supply the commercial market.

LIST OF STABLE ISOTOPES			
ISOTOPE	**PRIMARY METHOD OF ENRICHMENT**	**APPLICATION(S)**	**GENERAL COMMENTS**
Multiple isotopes with enrichments >99.9%	EMIS	- Forensic applications (DHS sponsored)	

Appendix 9: Response of the Isotope Program to the Recommendations of the 2009 NSACI Reports

We provide here a listing of the recommendations of the two 2009 NSACI reports and a summary of the actions taken by the Isotope Program in response to those recommendations. . The list was provided to NSACI (at our request) by the Isotope Program and reviewed by the subcommittee.

Report I [NSACI09] on Compelling Research Opportunities made six recommendations:

1. Invest in new production approaches of alpha-emitters with highest priority for ^{225}Ac. Extraction of the thorium parent from ^{233}U is an interim solution that needs to be seriously considered for the short term until other production capacity can become available.
   - ^{225}Ac
     - Continue to process the ^{229}Th for ^{225}Ac; up to about 360 mCi per year
     - R&D has been supported to demonstrate the viability of production of ^{225}Ac via high energy proton-induced spallation of ^{232}Th- targets
     - Developing production scale targets and processing techniques in order to implement regular and full-scale production of the isotope
     - "Projectized" ^{225}Ac multi-lab effort – review in October 2014, January 2015
   - ^{227}Ac
     - Separated and purified ^{227}Ac from surplus actinium-beryllium neutron sources at ORNL and other from legacy ^{227}Ac at PNNL
     - The ^{227}Ac can be used as a source (cow) for the decay production of very high purity ^{227}Th and ^{223}Ra, important alpha-emitting isotopes for medicine
     - Developing reactor-based production
   - ^{211}At
     - Developing Nation-wide production network (2013 - ~ 2016) at four institutions

2. We recommend investment in coordination of production capabilities and supporting research to facilitate networking among existing accelerators.
   - Restructured and increased the federal organization to provide more effective oversight
   - Created R&D Program – competitive (*e.g.*, FOA) at universities and labs and base program at labs
   - Development of university production capability and isotope production networks (such as ^{211}At)
   - Large Isotope Program Initiatives, including
     - Establish ^{241}Am production capability
     - ^{7}Li processing March 2014
     - BLIP Raster November 2013
     - ^{3}He equipment refurbishment
     - ^{252}Cf equipment refurbishment
     - ^{60}Co target design

3. We recommend the creation of a plan and investment in production to meet these research needs for heavy elements.
   - Worked with community to develop a plan for needed isotopes for superheavy physics program; ^{249}Bk produced and provided leading to the discovery of heavy elements
   - New contract for long-term supply of ^{252}Cf for Nation
     – ^{252}Cf equipment refurbishment October 2012
   - Re-establishing domestic ^{241}Am production

4. We recommend a focused study and R&D to address new or increased production of ^{3}He.
   - Isotope Program plays the lead role in Interagency He-3 Working Group- reports to White House National Security Staff.
   - DOE IP has supported initiatives at SRS to increase supply
   - Have provided technical expertise to NNSA and ARPAE for consideration of ^{3}He production R&D
   - Mitigation and prioritization efforts on behalf of the IAG have successfully addressed ^{3}He shortage

5. Research and Development efforts should be conducted to prepare for the reestablishment of a domestic source of mass-separated stable and radioactive research isotopes.
   - R&D invested to develop capability for enriched stable isotope production
   - ORNL ESIPF Pilot Plant project approved in December 2013

6. We recommend that a robust investment be made into the education and training of personnel with expertise to develop new methods in the production, purification, and distribution of stable and radio-active isotopes.
   - Have made investments in the support of students to participate in conferences and workshops
   - Have supported conferences, symposia and workshops in isotope production development
   - Training is considered in the selection of R&D awards
   - University isotope production sites being added in 2014; will include base funding

Then Report II [NSACI09A], the Long Range Plan for the (then) present progam, made nine recommendations for improving the program.

Six were for operations processes:

1. Maintain a continuous dialogue with all interested federal agencies and commercial isotope customers to forecast and match realistic isotope demand and achievable production capabilities.
   - Restructured and increased the federal organization to more effectively interface with stakeholders
   - Created the National Isotope Development Center
   - Annual survey to industrial customers on demand

- Annual federal workshops to assess isotope demand and promote communication regarding isotope supply and demand
- Improved communication, visibility with stakeholders – increased number of annual stakeholder meetings
- Increased presence and format of Isotope Booth at conferences
- Increased federal staff participation at conferences and workshops
- More frequent marketing assessments of individual isotopes
- Revamped the NIDC website to make more user friendly
- Regular publication of newsletters
- Creation of NIDC distribution list to advertise highlights, progress, challenges
- Regular attendance at CORAR meetings and participate in working group on industrial relations
- Lead for the White House NSS ^{3}He interagency Group on ^{3}He
- Member of OSTP Working Group on Critical Materials
- Member of OSTP working group on ^{99}Mo
- Lead for DOE-NIH Working Group on medical isotopes
- Member of NRC Task Force on Sealed Sources
- Member of NNSA Nuclear Materials Advisory Board
- Organize community workshops on isotopes of interest (for example ^{18}O)
- Organized internal federal working group on ^{7}Li
- Organized internal federal working group on ^{4}He recycling

2. Coordinate production capabilities and supporting research to facilitate networking among existing DOE, commercial, and academic facilities.
   - Created the National Isotope Development Center
   - Created R&D Program – competitive and base funded
   - Increased portfolio of isotope production sites
     - University sites being added in 2014
     - Addition of other DOE/NNSA sites, SRS, Y-12, ATR at INL
   - Supported R&D and production investments such as to facilitate production networks of individual isotopes (such as ^{211}At)
   - Stronger communication within program- bi-weeklies between HQ and NIDC; bi-weeklies at HQ, annual strategic planning meetings with sites, HQ and NIDC; monthlies between sites and HQ

3. Support a sustained research program in the base budget to enhance the capabilities of the Isotope Program in the production and supply of isotopes generated from reactors, accelerators, and separators.
   - Created base research programs at BNL, ORNL and LANL.

4. Devise processes for the Isotope Program to better communicate with users, researchers, customers, students, and the public and to seek advice from experts.
   - Improved communication, visibility with stakeholders
     - More frequent meetings
     - Formation of working groups (federal and with community)

  - Improve website to facilitate communication
  - Annual customer survey to obtain more information
  - Annual federal workshop and agency survey to obtain more information
  - More frequent individual market assessments
  - Created NIDC for more effective interface e with stakeholder
  - Added federal staff for more effective communication with stakeholders
- Introduced peer review into mode of operations and assessment of proposals to solicit expert advice
  - Peer review of R&D proposals
  - Peer review of isotope projects
  - Peer review of isotope facilities

5. Encourage the use of isotopes for research through reliable availability at affordable prices.
   - Increased portfolio of isotope production sites – production at universities introduces cost effectiveness and increased availability
   - Scrubbed production costs of all isotopes
   - Increased availability of research isotopes (increased scope of portfolio and/or increased supply)
   - Decreased price of research isotopes
     - Unit vs batch price for research isotopes

6. Increase the robustness and agility of isotope transportation both nationally and internationally.
   - NIDC has staff now dedicated to transportation
   - Formed Transportation Working Group (led by NIDC) to focus on transportation challenges

One aimed at developing a highly trained workforce for the future:

7. Invest in workforce development in a multipronged approach, reaching out to students, post-doctoral fellows, and faculty through professional training, curriculum development, and meeting/workshop participation.
   - Competitive R&D FOA and Core R&D funding provides for:
     - Support of postdocs
     - Succession planning
     - Workforce development is a priority in FOA
     - Support of students at university and lab sites
   - SC Early Career Awards also includes Isotope Program
   - Isotope Program participation in workshops, conference meetings
   - Sponsorship of Workshops and Symposia
   - Organization of Workshops and Symposia
   - NNSA Sponsored ^{99}Mo Topical Meetings (2011, 2013, 2014)

and two were on major investments in production capability

8. Construct and operate an electromagnetic isotope separator facility for stable and long-lived radioactive isotopes.
    - Transition from R&D 10mA EMIS at ORNL to prototype production facility (ESIPF)

9. Construct and operate a variable-energy, high-current, multi-particle accelerator and supporting facilities that have the primary mission of isotope production.
    - Seriously considered but did not implement
    - Industrial entities purchasing 70MeV cyclotrons
    - Cost prohibitive in times of fiscal constraint
    - More cost effective to invest in universities and establish production networks
    - Invest in capabilities that are unique to and more appropriately managed by the U.S. government